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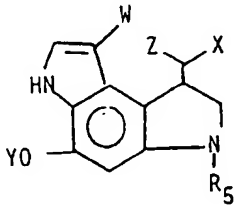

(I)

(57) Abstract

2-Acyl-4,5,8,8a-tetrahydro-4-oxycyclopropan[c]pyrrol(3,2-e) indole derivatives of Formula (I'). The compounds of Formula (I') are useful as uv light absorber substances, as chemical intermediates and as prodrugs of known spirocyclopropylpyrroloindole CC-1065 analogs. Representative Formula (I') compounds have been shown to possess useful ranges of antitumor activity in standard laboratory animal tests.

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NOVEL CC-1065 ANALOGS

BACKGROUND OF THE INVENTION

Antibiotic CC-1065, (7bR,8aS)-7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]1,6-dihydro-4-hydroxy-5-methoxy-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, is disclosed and claimed in L.J. Hanka et al U.S. Patent No. 4,169,888 together with a process for preparing antibiotic CC-1065 by aerobic fermentation procedures, and recovering antibiotic CC-1065 therefrom.

In The Journal of Antibiotics, 1985, 38, 746, D.G. Martin et al reported that acetic acid adds across the spirocyclopropylcyclohexadienyl (SCPCH) system of CC-1065 to produce the phenolic, acetic acid product (AAP), 7-[[7-[[1-[(acetyloxy)methyl]-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxybenzo[1,2-b:4,3-b']-dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide. AAP was tested in vitro and in vivo and found to be less potent than CC-1065 by a factor of 10^3 to 10^4 depending upon the particular test system and therefore tended to divert attention from adducts of the SCPCH system as useful antitumor agents or as prodrugs to CC-1065 analogs.

In J. Am. Chem. Soc., 103, No. 18, 1981, W. Wierenga published a "Synthesis of the Left-Hand Segment of the Antitumor Agent CC-1065".

EP Application 0 154 445 (published 11.09.85) discloses various analogs of antibiotic CC-1065, including compounds of formula EP-I and EP-II (see General Formula chart of EP 0154 445), wherein R_1 in formula EP-II is CH_3-, $-CH_2Ph$, $CH{=}CHCH_2$-, $-CH_2SCH_3$, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2CCl_3$, $-CH_2CH_2Si(R_2)_3$, or H, where Ph is phenyl; R is alkyl(C_1-C_5), phenyl, or H; R_2' is C_1 to C_5-alkyl, phenyl or hydrogen, and is not necessarily the same as R in one compound; R_3 is alkyl(C_1-C_5), phenyl, or H; and X is Cl, Br, or I-, or OSO_2R_4O, where R_{40} is C_1 to C_5-alkyl, phenyl, tolyl, bromophenyl, nitrophenyl, or trifluromethyl. The O-protected compounds of formula EP-II are chemically stable and only removable under specific chemical conditions. However, when the compounds of formula EP-II are O-deprotected, they can be cyclized to yield the compounds of EP-I.

SUMMARY OF THE INVENTION

This invention provides some new synthetically obtained 2-acyl-4,5,8,8a-tetrahydro-4-oxocyclopropan(c)pyrrolo(3,2-e) indole derivative compounds of formula I' (see General Formulae Chart), as defined hereinafter, which are useful as uv light absorber substances, or as chemical intermediates and as prodrugs for known spirocyclopropylpyrroloindole CC-1065 analogs. Representative formula I' compounds have also been shown to possess useful ranges of antitumor activity in standard laboratory animal tests. Compounds of formula I', where X is halogen and Z is hydrogen, are useful as antibacterial compounds. The compounds of this invention are obtained by chemical processes shown in Chart A and detailed in the examples.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, this invention provides new chemical compounds of general Formula I' (see GENERAL FORMULA sheet) wherein W is selected from C_1-C_5 alkyl, phenyl or hydrogen;

wherein X is selected from azido, a halogen atom, cyanate, thiocyanate, isocyanate, thioisocyanate, phosphate diester ($-PO(OR)_2$), phosphonyl ($-O-PO_2R$), thiophosphonyl (-O-PSOR), sulfinyl (-O-SOR) or sulfonyl ($-O-SO_2R$);

wherein Y is selected from hydrogen, -C(O)R, -C(S)R, $-C(O)OR_1$, $-S(O)_2R_1$, $-C(O)NR_2R_3$, $-C(S)NR_2R_3$, or $-C(O)NHSO_2R_4$; with the proviso that when X is a bromo, chloro or iodo atom, Y is not hydrogen;

wherein Z is selected from the group consisting of C_1-C_5 alkyl, phenyl or hydrogen;

wherein R is selected from the group consisting of C_1-C_{20} alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_1 is selected from C_1-C_{20} alkyl or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

wherein R_2 and R_3, being the same or different, are selected from hydrogen, C_1-C_{20} alkyl, or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; with the proviso that both R_2 and R_3 can not be phenyl or substituted phenyl;

wherein R_4 is selected from C_1-C_{10} alkyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_5 is an acyl group selected from the group consisting of a compound of formula (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x), (xi), (xii), (xiii), (xiv), (xv), (xvi), (xvii), (xviia), (xviib), (xviii), (xix), (xx), (xxi), (xxii) as defined in Chart C, and when any of X_1 to X_6 is OH or NH_2, then each of the R_5 groups represented by (ii), (vi), (viii), (ix), (x), (xvii), (xviia), (xviib), (xviii), (xix), (xx), (xxi) or (xxii) may be coupled with each other forming the dimer combinations set forth in Chart D, wherein the respective R_5 groups are bound together via an oxycarbonyl (-OOC-) or an amide (-NHCO-) linkage.

Illustrative examples of the thus formed dimer are given in Chart E.

W is preferably methyl.

X is preferably halogen, more preferably chloro or bromo.

Y is preferably -COR, wherein R is selected from C_1-C_{10} alkyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; $-C(O)NHSO_2R_4$; or $-C(O)NR_2R_3$.

Z is preferably hydrogen.

R_5 is preferably the dimer combination viii + xviib bound together with the amide linkage.

An embodiment of this invention are the new compounds of general formula I' wherein Y is selected from hydrogen, -C(O)R,-C(S)R,C(O)OR_1, $-S(O)_2R_1$, $-C(O)NR_2R_3$, $-C(S)NR_2R_3$, or $-C(O)NHSO_2R_4$; with the proviso that when X is a halogen atom, Y is not hydrogen.

Halogen atom (halo) refers to a bromo, chloro, iodo or fluoro atom.

Examples of C_1-C_{20} alkyl are methyl, ethyl, propyl, butyl and the like, including isomeric forms thereof. Examples of C_1-C_3 alkoxy are methoxy, ethoxy, propoxy and isomeric forms thereof. Examples of C_2-C_6 dialkylamino are dimethylamino, diethylamino, methylethylamino, dipropylamino and ethylpropylamino. Examples of aminocarbonylalkyl-(C_1-C_{10}) are aminocarbonylpentyl ($-NHCOC_5H_{11}$) and aminocarbonylmethyl

(-$NHCOCH_3$).

The compounds of formula I' on the GENERAL FORMULA sheet can be named as derivatives of the numbering system (B') shown on the GENERAL FORMULA sheet. Such compounds will contain the 1,2,3,6-tetrahydro-3-R_5-8-W-5-Y-benzo[1,2-b:4,3-b']dipyrrol-1-[Z-CH(X)]-structure.

The compounds of Formula I' are drawn as the racemic mixture and include the natural isomer of Formula I'a which can be resolved from the racemic mixture and/ or prepared from starting materials of the natural, i.e. 1(S)-configuration.

Examples of Formula I' compounds of this invention include:

(S)-N-[2-[[5-(acetyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-1H-indole-2-carboxamide (Cpd #1);

(S)-N-[2-[[5-(acetyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-2-benzofurancarboxamide (Cpd #2A);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H]indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate (Cpd #2B);

(S)-N-[2-[[5-(benzoyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #2C);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl tetradecanoate (Cpd #2D);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl decanoate (Cpd #2E);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl dodecanoate (Cpd #2F);

(S)-N-[2-[[1-(azidomethyl)-1,6-dihydro-5-hydroxy-8-methyl-benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #6);

(S)-N-[2-[[5-(benzoyloxy)-1-(bromomethyl)-1,6-dihydro-8-methyl-benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl] 2-benzofurancarboxamide (Cpd #2G);

(S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl decanoate (Cpd #3);

(S)-6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl tetradecanoate (Cpd #4);

(S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate (Cpd #5);

butyl 1-ethyl-3,6,7,8-tetrahydro-6-[[5-[(2-quinolinyl-carbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(thiocyanatomethyl)benzo[1,2-b:4,3-b']dipyrrol-4-yl carbamate;

O-[8-(bromoethyl)-3,6,7,8-tetrahydro-6-[[5-[(2-quinoxalinyl-carbonyl)amino]-2-benzofuranyl]carbonyl]benzo[1,2-b:4,3-b']dipyrrol-4-yl] O-phenyl thiocarbamate;

O-[8-ethyl-3,6,7,8-tetrahydro-1-methyl-6-[[6-methyl-1H-indol-2-yl)carbonyl]amino]-2-quinolinyl]carbonyl]benzo[1,2-b:4,3-b']dipyrrol-4-yl] O-(1-methylethyl) thiocarbamate;

4-nitro-2-[[1-(azidomethyl)-1,6-dihydro-8-methyl-5-[(methyl-sulfonyl)oxy]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl 1H-pyrrole-2-carbamate;

5,6,-dimethyl-2-[[1-(fluoromethyl)-1,6-dihydro-5-[[(4-methyl-phenyl)sulfonyl]oxy]-8-propylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-6-quinoxalinyl 2-benzofurancarbamate;

O-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl] butylthiocarbamate;

methylphenyl-O-[8-(bromomethyl)-3,6,7,8-tetrahydro-6-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-benzimidazo]-2-yl]carbonyl]benzo[1,2-b:4,3-b']dipyrrol-4-yl] thiocarbamate;

N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenylamino)-carbonyl]oxy]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-

indol]-5-yl]-2-benzofurancarboxamide;

[3-[[5-[[(6,7-dichloro-2-benzofuranyl)carbonyl]amino]-2-benzoazolyl]carbonyl]-1,2,3,6-tetrahydro-5-[[(phenylamino)carbonyl]oxy]-benzo[1,2-b:4,3-b']dipyrrol-1-yl]methyl cyanate;

N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(methylamino)-carbonyl]oxy]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-5-benzothiazolyl]-5-(trifluoromethyl)-2-benzoxazolecarboxamide;

(S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenyl-amino)carbonyl]oxy]benzo[1,2-b:4,3-b']dipyrrol-3(2)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #10A).

(S)-3-[[6-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, butyl carbamic acid (Cpd #10B);

(S)-3-[[6-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 3,4-b']dipyrrol-4-yl ester, 2,2-dimethyl propanoic acid (Cpd #10C);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, [4-(trifluoromethyl)phenyl]-carbamic acid (Cpd #10D);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-2-methyl]benzo [1,2-b 4,3-b']dipyrrol-4-yl ester, (3,5-dimethylphenyl)-carbamic acid (Cpd #10E);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, (4-chlorophenyl)-carbamic acid (Cpd #10F);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, (3,4-difluorophenyl)-carbamic acid (Cpd #10G);

(S)-8-(chloromethyl)-6-[[5-[[[6-(diethylamino)-2-benzofuranyl]-carbonyl]amino]-1H-indol-2-yl]carbonyl]-3,6,7,8-tetrahydro-1-methyl-benzo[1,2-b 4,5-b']dipyrrol-4-yl ester, 2,2-dimethyl-propanoic acid (Cpd #11A);

(S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenyl-amino)carbonyl]oxy]benzo[1,2-b 4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-

indol-5-yl]-6-(diethylamino)-2-benzofurancarboxamide (Cpd #11B).

The compounds of Formula I' are readily prepared by reacting the appropriate spirocyclopropylcyclohexadienyl analog (Formula I) with the Y-X reagent (Chart A) or with H-X and then acylating with Y-X' (Chart A') where X' is an active leaving group, for example halide, azide, sulfonate, and the like. The starting spirocyclopropylcyclohexadienyl analog (Formula I) is dissolved in an inert solvent such as methylene chloride, tetrahydrofuran (THF), N,N-dimethylformamide (DMF, DMFA), dimethylacetamide (DMA), pyridine, dioxane, N-methylpyrrolidone and the like. The resultant solution is treated with the reagent Y-X (where X and Y as defined above) and the solution stirred at ambient temperature until thin layer chromatography (TLC) shows the reaction to be complete (normally for reactive acyl halides in a few minutes but for weak acids or acylating agents a few hours or days may be required. For very reactive reagents the temperature may be lowered to -20°C or less and for relatively unreactive addents the temperature may be raised to 80°C or higher depending upon the solvent). When the reaction is complete, the solution is diluted with an appropriate solvent (methylene chloride, ethyl acetate, ether, THF (with brine), and the like. The organic layer is extracted with a mild base such as sodium or potassium bicarbonate, washed with water, dried by a suitable drying agent such as anhydrous magnesium sulfate or anhydrous sodium sulfate. Filtration of the drying agent and evaporation of the solvent leaves the desired product (Formula I') which may be used as such or purified by crystallization or chromatography by methods well know to those skilled in the art.

Example 1 Preparation of (S)-N-[2-[[5-(acetyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-1H-Indole-2-carboxamide; Cpd #1

15mg (0.028 mmol) of (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indo-5-yl]-1H-Indole-2-carboxamide is dissolved in 2 ml of dry pyridine at 5°C, degassed with nitrogen and treated with 0.005 ml of acetyl chloride. After 30 min. at 5°C, the solution is warmed to room temperature, quenched with 1 ml of water, diluted with 50 ml of ethyl acetate, and washed with two 20 ml portions of 1:1 brine/1N hydrochloric acid, and then brine. The solution is dried with sodium

sulfate, filtered, adsorbed on 1 g of Celite™, and flash chromatographed on 10 g of silica gel, eluting with 50% ethyl acetate in hexane to give in fractions (25 ml) 6-12 the title compound as a solid.

NMR: (d6-acetone, δ) 2.3 (s,3H); 2.4(d,3H); 3.6-3.8 (m,1H); 3.9-4.3 (m,2H); 4,6-5.0 (m,2H); 7.0-7.8 (m,9H); 8.1 (s,1H); 8.4 (s,1H); 9.7 (s,1H); 10.4 (s,1H); 11.0 (s,1H); 11.1 (s,1H).

M.S. (FAB) Calcd for $C_{32}H_{26}ClN_5O_4$: 579.1673; Found: 579.1662

UV:MeOH λmax 311; α 82; ε 47,800.

Example 2 Reaction of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide with acid chlorides

A 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide is dissolved in 150 μl pyridine. 2 equivalents of the acid chloride or bromide is added and the reaction mixture stirred for 5-30 minutes under nitrogen at room temperature. The reaction progress is checked by HPLC or TLC. When completed, one drop of water is added and everything evaporated under vacuum. The crude product is chromatographed over 100 to 1 silica gel, eluting with acetone-hexane. 0.5/1.0 ml fractions are collected and analyzed by TLC. The fractions containing product are combined and evaporated to yield the desired compound.

Example 2A Preparation of (S)-N-[2-[[5-(acetyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-2-benzofurancarboxamide (Cpd #2A)

Following the general procedure of Example 2, 3 μl of acetyl chloride is added to a 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved in 150 μl pyridine. The reaction is stirred for 5 min under nitrogen at room temperature. One drop of water is added and everything evaporated under vacuum. The crude product is chromatographed over 1 g silica gel, eluting with 20 ml acetone-hexane (40/60), 10 ml (50/50) and 10 ml (60/40); R_f0.71. The 0.5ml fractions (13-28) containing the title compound are combined and evaporated. The crude product is purified on reverse phase C18 with methanol-water (80/20);

TLC (silica gel): R_f=0.71 in acetone-hexane (50/50).

NMR: (d6-acetone, δ) 2.344 (s,3H); 2.432 (d,3H); 3.62-3.75 (dd,1H); 3.91-4.04 (dd,1H); 4.12-4.29 (m,1H); 4.69-4.88 (m,2H); 7.145 (d,1H); 7.21 (s,1H); 7.30-7.71 (m,6H); 7.77-7.82 (dd,1H); 8.02 (s,1H); 8.36-8.40 (m,1H); 9.83 (s,1H).

Example 2B Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H]indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate (Cpd #2B).

Following the general procedure of Example 2, 5 μl of hexanoyl chloride is added to a 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved in 150 μl pyridine. The reaction is stirred for 15 min under nitrogen at room temperature. One drop of water is added and everything evaporated under vacuum. The crude product is coated on 100 mg of silica gel, placed on a 1.5 g silica gel column and eluted with hexane-acetone (40/60). The 0.5ml fractions (9-15) containing the title compound are combined and evaporated to yield the title compound.

TLC (silica gel): R_f=0.76 in acetone-hexane (50/50).

NMR: (d6-acetone, δ) 0.89-1.02 (t,3H); 1.30-1.50 (m,6H); 1.71-1.88 (q,2H); 2.74 (t,2H); 3.66-3.80 (dd,1H); 3.97-4.08 (dd,1H); 4.20-4.34 (m,1H); 4.80-4.94 (m,2H); 7.19 (bs,1H); 7.25-7.29 (d,1H); 7.34-7.77 (m,6H); 7.81-7.89 (d,1H); 8.10 (s,1H); 8.45 (s,1H); 9.77 (s,1H); 10.27 (bs,1H); 10.95 (bs,1H).

Example 2C Preparation of (S)-N-[2-[[5-(benzoyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #2C).

Following the general procedure of Example 2, 6 μl of benzoyl chloride is added to a 11 mg (0.022 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved in 150 μl pyridine. The reaction is stirred for 10 min under nitrogen at room temperature. One drop of water is added and everything evaporated under vacuum. The crude product is coated on 100 mg of silica gel, placed on a 1.5 g silica gel column and eluted with hexane-acetone (40/60). The 0.5ml fractions (9-22) containing the title compound are combined and evaporated to yield the title compound.

TLC (silica gel): R_f=0.34 in acetone-hexane (40/60).

NMR: (d6-acetone, δ) 2.48 (s,3H); 3.68-3.83 (dd,1H); 3.97-4.10 (dd,1H); 4.20-4.36 (m,1H); 4.77-4.93 (m,2H); 7.17 (bs,1H); 7.24-7.29 (d,1H); 7.32-7.77 (m,9H); 7.78-7.86 (d,1H); 8.02-8.11 (m,1H); 8.20-8.32 (m,2H); 8.44 (s,1H); 9.66 (bs,1H); 10.52 (bs,1H); 10.97 (bs,1H).

Example 2D Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl tetradecanoate (Cpd #2D);

Following the general procedure of Example 2, 10 μl of myristoyl chloride is added to a 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved in 150 μl pyridine. The reaction is stirred for 5 min under nitrogen at room temperature. One drop of water is added and everything evaporated under vacuum. The crude product is coated on 100 mg of silica gel, placed on a 1.5 g silica gel column and eluted with hexane-acetone (70/30). The 1 ml fractions (9-14) containing the title compound are combined and evaporated to yield the title compound.

TLC (silica gel): R_f=0.65 in acetone-hexane (30/70).

NMR: (d6-acetone, δ) 0.85-0.96 (t,3H); 1.24-1.54 (m20H); 1.72-1.88 (q,2H); 2.47 (s,3H); 2.68-2.80 (t,2H); 3.64-3.80 (dd,1H); 3.96-4.08 (dd,1H); 4.20-4.32 (m,1H); 4.76-4.94 (m,2H); 7.12 (s,1H); 7.27 (s,1H); 7.35-7.77 (m,6H); 7.80-7.88 (d,1H); 8.10 (s,1H); 8.47 (s,1H); 9.70 (s,1H); 10.25 (bs,1H); 10.99 (bs,1H).

Example 2E Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl decanoate (Cpd #2E);

Following the general procedure of Example 2, 9 μl of decanoyl chloride is added to a 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved in 150 μl pyridine. The reaction is stirred for 30 min under nitrogen at room temperature. One drop of water is added and everything evaporated under vacuum. The crude product is coated on 100 mg of silica gel, placed on a 1.2 g silica gel column and eluted with hexane-acetone (60/40). The 1 ml fractions (8-16) containing the title compound are combined and evaporated to yield the title

compound. The more polar chlorophenol is eluted with hexane-acetone (50/50), fractions collected and evaporated, added to 100 µl pyridine and 5 µl decanoyl chloride for 30 min. Worked up as above. The product in fractions (5-13) is combined with the initial crop (fractions 8-16) to yield a total of 8 mg. of title compound.

TLC (silica gel): R_f=0.69 in acetone-hexane (40/60).

NMR: (d6-acetone, δ) 0.84-0.98 (t,3H); 1.25-1.53 (m,12H); 1.72-1.88 (q,2H); 2.484 (d,3H); 2.67-2.80 (t,2H); 3.66-3.80 (dd,1H); 3.97-4.10 (dd,1H); 4.20-4.33 (m,1H); 4.76-4.94 (m,2H); 7.16 (s,1H); 7.27 (s,1H); 7.34-7.77 (m,6H); 7.81-7.88 (d,1H); 8.09 (s,1H); 8.44 (d,1H); 9.75 (s,1H); 10.27 (bs,1H); 10.85 (bs,1H).

Example 2F Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl dodecanoate (Cpd #2F);

Following the general procedure of Example 2, 10 µl of lauroyl chloride is added to a 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved in 150 µl pyridine. The reaction is stirred for 5 min under nitrogen at room temperature. The reaction mixture is diluted with acetone and evaporated under vacuum. The crude product is coated on 150 mg of silica gel, placed on a 1.5 g silica gel column and eluted with hexane-acetone (70/30). The 1 ml fractions (6-9) containing the title compound are combined and evaporated to yield the title compound.

TLC (silica gel): R_f=0.70 in acetone-hexane (40/60).

NMR: (d6-acetone, δ) 0.84-0.97 (t,2H); 1.24-1.53 (m,16H); 1.72-1.89 (q,2H); 2.475 (d,3H); 2.68-2.80 (t,2H); 3.66-3.80 (dd,1H); 3.96-4.08 (dd,1H); 4.18-4.33 (m,1H); 4.74-4.94 (m,2H); 7.16 (s,1H); 7.27 (s,1H); 7.35-7.76 (m,6H); 7.82-7.88 (dd,1H); 8.10 (s,1H); 8.45 (d,1H); 9.73 (s,1H); 10.26 (bs,1H); 10.95 (bs,1H).

Example 2G Preparation of (S)-N-[2-[[5-(benzoyloxy)-1-(bromomethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl] 2-benzofurancarboxamide (Cpd #2G);

Following the general procedure of Example 2, 5 µl of benzoyl bromide is added to a 10 mg (0.02 mmol) quantity of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide dissolved

in 150 μl pyridine. The reaction is stirred for 15 min under nitrogen at room temperature. One drop of water is added and everything evaporated under vacuum. The crude product is coated on 150 mg of silica gel, placed on a 1.3 g silica gel column (80/20 hexane-acetone) and eluted with a gradient of hexane-acetone (80/20 to 40/60). The 0.5 ml fractions (25-30) containing the title compound are combined and evaporated to yield the title compound.

TLC (silica gel): R_f=0.55 in acetone-hexane (50/50).

NMR: (d6-acetone, δ) 2.483 (s,3H); 3.57-3.72 (t,1H); 3.88-3.99 (dd,1H); 4.23-4.42 (m,1H); 4.76-4.93 (m,2H); 7.17 (s,1H); 7.24 (s.1H); 7.32-7.78 (m,9H); 7.78-7.87 (d,1H); 8.17-8.32 (m,3H); 8.43 (s,1H); 9.67 (s,1H); 10.53 (bs,1H); 10.95 (bs,1H).

Example 3 Preparation of (S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]-carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl decanoate (Cpd #3);

CC-1065 (10.4 mg, 0.015 mM) is dissolved in pyridine (150 μl) and put under an atmosphere of nitrogen. Decanoyl chloride (10 μl) is added, and the reaction is stirred at room temperature for 50 minutes. The crude solid product is obtained by precipitation with water and centrifugation. It is purified by column chromatography on 2 g of silica gel in (14-86) dimethylformamide toluene. Fractions are of one or two ml. The desired product, found in fractions 7-15, weight 7.1 mg (54% yield).

TLC (silica gel): R_f=0.54 in DMF-toluene (14/86).

MS(FAB): Calcd. for $C_{47}H_{52}ClN_7O_9$: 893.3515

Measured: 893.3472.

Example 4 Preparation of (S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]-carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl myristoate (Cpd #4);

A 9.9 mg (0.014 mM) quantity of CC-1065 in dry pyridine (150 μl) under nitrogen is treated with myristoyl chloride (9 mg, 0.036 mM). After stirring three hours at room temperature the product is precipitated with water, and isolated by centrifugation. The solid (16 mg) is chromatographed on a 2.5 g silica gel column. Fractions

of 1-2 ml are collected. Elution with (13-87) and (25-75) DMF toluene brought the product off in fractions 11-19. An 11% yield (1.5 mg) is obtained.

TLC (silica gel): R_f=0.63 in DMF-toluene (13/87).

MS(FAB): Calcd. for $C_{51}H_{61}ClN_7O_9$: 950.4219

Measured: 950.4175

Example 5 Preparation of (S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]-carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate (Cpd #5);

An 11 mg (0.016 mmole) quantity CC-1065 is dissolved in 150 µl pyridine. Add 4 µl hexanoyl chloride and follow the reaction by HPLC. Two more 4 µl portions of hexanoyl chloride are added after 35 and 70 minutes reaction time. (The reaction to the intermediate chlorophenol is fast but acylation to the desired hexanoate is not only slow but also not entirely selective since an even less polar product appears before all the chlorophenol has been converted to the desired hexanoate.) After a total of 3 hours reaction, the mixture is transferred to a conical test tube, and washed with 100 µl pyridine. Then 5 ml water is added and a solid precipitates. The solid is spun down in a centrifuge and the liquid phase removed. This procedure is repeated with 5 ml water and 1.5 ml methanol. The solid is then dried under vacuum. HPLC of the 3 washes shows only small amounts of material present as a mixture of product and less polar side product.

The solid residue is chromatographed over 2 g of silica gel 60 eluted with (20-80) acetone-methylene chloride. Two ml fractions are collected. Impure product is found in fractions 5-9. This material is rechromatographed over silica gel 60, this time eluting with 15 ml of (10-90) DMF-toluene and ad lib with (15-85) DMF-toluene. Two ml fractions are collected. The product is found by TLC in fractions 21-25 .

TLC (Silica Gel GF): R_f = 0.50 in (20-80) acetone-methylene chloride

R_f = 0.33 in (15-85) DMF-toluene.

Example 6 Preparation of (S)-N-[2-[[1-(azidomethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-

indol-5-yl]-2-benzofurancarboxamide; (Cpd #6) from (7bR)-N-[2-[(4,5,-8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (73975)

A solution of hydrogen azide is prepared by treating a mixture of sodium azide (1.0 g, 15 mM), water (1 ml), and methylene chloride (7 ml) at 0 C with concentrated sulfuric acid (0.42 ml, 8 mM). After approximately 20 minutes, the methylene chloride solution is decanted from the solids. The solution is dried over anhydrous sodium sulfate and treated with 1,1,3,3-tetramethylguanidine (71 mg, 0.62 mM) to give a salt-acid mixture.

A 9.9 mg quantity (0.02 mM) of (7bR)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (U-73975) is treated with 0.5 ml of the hydrogen azide solution. After stirring in the dark at room temperature for 1.5 hours, the reaction is evaporated under a nitrogen stream. The residue is purified on a 2.5 g reversed phase C_{18} column. Eluents are (65-35) through (76-24) DMF-water. Fractions of 3-4 ml are collected. The product is found in fractions 17-19. It is crystallized from acetone-hexane. A 41% yield of crystals (4.5 mg) is obtained, while the mother liquors contained 4 mg of crude material. Both the crystalline product and mother liquors are re-chromatographed, each on 0.8 g of silica gel, in (40-60) acetone-hexane. The desired product is slowly crystallized from acetone-hexane. A 2.2 mg quantity of the pure azide analog is obtained.

MS (FAB), before re-purification: Calcd. for $C_{30}H_{23}N_7O_4$: 545.1811; Measured: 545.1795.

TLC (silica gel GF): R_f = 0.26 in (40-60) acetone-hexane, R%f of chlorophenol = 0.22 in same.

The O,N-bisacylated compounds of Formula I' can also be prepared in a single step as illustrated in Chart A" and Examples 7 and 8.

Example 7 Preparation of (S)-6-hexanoyl-8-chloromethyl-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate; O,N-bis(hexanoyl)CPI

A solution of 0.5 mg (0.002 mM) of CPI and 4-dimethylamino-pyridine (one crystal) in dry pyridine is cooled to -78° under argon. Hexanoyl chloride (1μl, 0.007 mM) is added and the reaction is maintained at 0°C for two days. A similar reaction with CPI in acetone with K_2CO_3 as the base gives the same product. The products

are diluted with methylene chloride, combined, and washed with water and 5% sodium bicarbonate solution. The aqueous layers are reextracted. Drying and concentration of the combined organic solutions give 6.5 mg of crude product. It is purified by preparative thin layer chromatography on a 5x17 cm. Analtech analytical plate, with (40-60-0.2) acetone-skellysolve B-triethylamine as the eluant. The desired product band is visualized by uv light, scraped off the plate into a scintered glass funnel, and eluted with (50-50) acetone-methylene chloride. Solvent evaporation leaves the product, (S)-6-hexanoyl-8-chloromethyl-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate.

NMR ($CDCl_3$, TMS): δ0.77-0.893 (M,6H); 1.26-1.38, (M,8H); 1.66-1.75 (m,4H); 2.20-2.40 (m, 1H); 2.34 (d, 3H); 2.44-2.50 (m,1H); 2.53-2.56 (t,2H); 3.32 (t,1H); 3.74-3.77 (m,1H); 3.89-3.92 (m,1H); 4.06-4.10 (m,1H); 4.23(dd,1H); 6.91(s); 7.80(s); 8.01(s).

Example 8 Preparation of (S)-6-(4-chlorobenzoyl)-8-chloromethyl-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl 4-chlorobenzoate

To a 11.2 mg (0.056 mmol) of natural CPI is added 19.2 ml of 7.2 millimolar triethylamine in methylene chloride (0.138 mmol) and 17 ml of 7.9 millimolar chlorobenzoyl chloride in methylene chloride (0.134 mmol). After 1.5 hr stirring at room temperature in subdued light, TLC densitometry (Whatman LKC18D) indicates the absence of CPI and the presence of a clean lipophilic component at Rf 0.3 (acetone-water 3:1). After overnight storage in the freezer, the solution is evaporated to dryness and the residue triturated with 3 ml of 85% methanol (aqueous). The suspension is briefly chilled and the solid collected, washed with 5 ml of 85% methanol in portions, and dried affording 30.7 mg of homogeneous diacylated product, TLC densitometry R_f 0.31 on C18 with 3:1 acetone-water monitored by 250 nm UV light.

UV: $\lambda^{doxane}/_{max}$ nm (ε) end abs., 243 (51,550), 271 (sh 21,750), 307 (sh 11,750) CD in dioxane: nm (molar ellipticity) 300 (-9,000), 250 (+ 18,000) 228 (-43,000) FAB-MS: m/z 513 $(M + H)_+$.

Example 9 Preparation of (S)-N-[2-[[5-phenylaminocarbonyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-2-benzofurancarboxamide. (Cpd 10A)

A 10 mg (0.019 mM) quantity of (S)-N-[2-[[5-hydroxy-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-

yl]carbonyl]-1H-indol-5-yl-2-benzofurancarboxamide is dissolved in freshly distilled THF and the solution stirred under nitrogen at 25° C. To the solution is added 2 microL (0.019 mM) of phenylisocyanate (PIC) and 0.5 microL of triethylamine (TEA). After stirring 18 hrs. the reaction is treated with an additional 1 microL of PIC. The reaction is then stirred another 72 hrs, at which time 0.5 microL more of TEA is added. After another 18 hrs. the reaction mixture is added to 200 mg of silica gel and evaporated under vacuum. The residue is placed on the top of 2 g of silica gel and eluted with acetone-hexane (30/70) followed by acetone-hexane (50/50). The fractions containing product, as found by TLC, are combined and concentrated giving the title compound.

TLC (silica gel): R_f=0.51 in acetone-hexane (40/60).

Mass Spectrum (FAB): 658, 539, 303, 237, 236, 187, 145.

The urethane-hydrochloride analogs can be prepared by reacting the appropriate chlorophenol analog (Formula II) with the appropriate isocyanate (Chart A'''). The starting chlorophenol analog (Formula II) is dissolved in the dark in an aprotic solvent(s) such as methylene chloride, tetrahydrofuran (THF), dioxane, toluene or combination thereof. To the resultant solution is added the appropriate isocyanate and a tertiary amine base such a as triethylamine, diisopropylethylamine or pyridine, and the like. The reaction mixture is stirred at ambient temperature until thin layer chromatography (TLC) shows the reaction to be complete (normally for reactive isocyanates in a few minutes but for weak agents a few hours or days may be required. For very reactive reagents the temperature may be lowered to -20°C or less and for relatively unreactive addents the temperature may be raised to 80°C or higher depending upon the solvent). When the reaction is complete, the reaction mixture is evaporated and the residue chromatographed over silica gel, eluting, for example with increasing concentrations of acetone in n-hexane. Fractions containing the desired product are identified by TLC, combined and evaporated to give the urethane analog.

Example 10 Reaction of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]-carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide with isocyanates

A 0.015 mmol quantity of (S)-N-[2[[21-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-

indole-5-yl]-2-benzofurancarboxamide is dissolved in the dark in 1.0ml of freshly distilled THF. Six equivalents of the isocyanate and 2 equivalents triethylamine (NEt_3) is added and the reaction mixture stirred from 1 hour to 30 days under nitrogen in the dark at room temperature. The reaction progress is checked by HPLC or TLC. When completed, the crude product is chromatographed over 100 to 1 silica gel, eluting with acetone-hexane. 0.5/1.0 ml fractions are collected and analyzed by TLC. The fractions containing product are combined and evaporated to yield the desired compound.

Example 10A Preparation of (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenylamino)carbonyl]oxy]benzo[1,2-b:4,3-b']dipyrrol-3(2)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #10A).

Following the general procedure of Example 10, 16 mg (0.14 mmol) of phenyl isocyanate and 4 mg (0.036 mmol) triethylamine is added to a 10 mg (0.019 mmol) quantity of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]-carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide dissolved in the dark in 0.5 ml of THF. The reaction is stirred in the dark for 41 days under nitrogen at room temperature. The crude product is chromatographed over 2 g silica gel, eluting with acetone-hexane (30/70 and 50/50). The fractions containing the title compound are combined and evaporated.

TLC (silica gel): 40% acetone - 60% hexane; Rf 0.50.

NMR: acetone: 2.45 (s, 3H); 3.63-3.77 (dd, 1H); 3.93-4.05 (dd, 1H); 4.15-4.30 (t, 1H); 4.68-4.90 (m, 2H); 7.00-7.12 (t, 1H); 7.17 (s, 1H); 7.22 (s, 1H); 7.28-7.41 (m, 3H); 7.43-7.50 (dd, 1H); 7.50-7.56 (dd 1H); 7.56-7.70 (m, 5H); 7.76-7.84 (dd, 1H); 8.13 (s, 1H); 8.37 (d, 1H); 9.41 (bs, 1H); 9.81 (bs, 1H); 10.5 (bs, 1H); 10.96 (bs, 1H);

MS: $[M+H]^+$ at 658,660.

Fragment ions at 539, 303, 237, 236, 187 and 145.

Example 10B Preparation of (S)-3-[[6-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, butyl carbamic acid (Cpd #10B).

Following the general procedure of Example 10, 11 mg 0(.11 mmol) of butyl isocyanate and 3 mg (0.029 mmol) NEt_3 is added to a 20 mg

(0.038 mmol) quantity of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide dissolved in the dark in 1 ml of THF. The reaction is stirred in the dark for 11 days under nitrogen at room temperature. The crude product is chromatographed over 3 g silica gel, eluting with acetone-hexane (40/60). The fractions containing the title compound are combined and evaporated. The product is further purified on 4 g silica gel, eluting with 30% ethyl acetate (EtOAc) - 70% toluene.

TLC (silica gel): 30% EtOAc - 70% toluene; Rf 0.38.

NMR: Acetone, TMS. 0.89 (t, 3H); 1.4-1.55 (m, 2H); 1.55-1.70 (m, 2H); 2.29 (s, 3H); 3.43 (6S, 2H); 3.59 (t, 1H); 3.85-4.0 (m, 1H); 4.10-4.25 (m, 1H); 4.65-4.90 (m, 2H); 7.20 (s, 1H); 7.36 (t, 1H); 7.4-7.7 (m, 6H); 7.78 (d, 1H); 7.97 (s, 1H); 8.64 (6s, 1H); 9.35 (6s, 1H); 10.11 (6s, 1H); 11.22 (6s, 1H).

MS: $[M-H]^+$ at 638.640.

Fragment ions at 539, 538, 489, 303, 236, 235, 199, 187 and 145.

Example 10C Preparation of (S)-3-[[6-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 3,4-b']dipyrrol-4-yl ester, 2,2-dimethyl propanoic acid (Cpd #10C).

A 15 mg (0.03 mmol) quantity of (7bR)-N-[2-[[4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide is dissolved at 25°C in 200 microL of dry pyridine and the solution treated with 8 microL of pivaloyl chloride. After 30 min the reaction is treated with 1 drop of water and evaporated under vacuum. The residue is coated on 250 mg of silica gel and placed on top of a 2.5 g silica gel column. The column is eluted with acetone-hexane (40/60). The 1.5 mL fractions (8-12) containing the title compound are combined and evaporated to yield 10 mg of the title compound.

TLC (silica gel): 50% acetone - 60% hexane; Rf 0.45.

NMR: Acetone, TMS.

1.43 (s, 9H); 2.45 (s, 3H); 3.66-3.77 (dd, 1H); 3.95-4.04 (dd, 1H); 4.18-4.30 (t, 1H); 4.73-4.90 (m, 2H); 7.11 (s, 1H); 7.22 (s, 1H); 7.32-7.40 (t, 1H); 7.45-7.53 (t, 1H); 7.55-7.71 (m, 4H); 7.78-7.83 (d, 1H); 8.04 (s, 1H); 4.40 (s, 1H); 9.75 (s, 1H); 9.99 (s, 1H); 10.90 (s, 1H).

MS: $[M-H]^+$ at 623, 625; $[M]^+$ at 622, 624. Measured: 623.2047; theory for $C_{35}H_{32}ClN_4O_5$: 623.2061.

Other fragment ions: 539, 320, 303, 237, 236, 199, 187, 145 and 57.

Example 10D Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, [4-(trifluoromethyl)-phenyl]-carbamic acid (Cpd #10D).

Following the general procedure of Example 10, 40 mg (0.21 mmol) of 4-trifluoromethylphenyl isocyanate and 7 mg (0.072 mmol) triethylamine is added to a 20 mg (0.038 mmol) quantity of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide dissolved in the dark in 1 ml of THF. The reaction is stirred in the dark for 6 days under nitrogen at room temperature. The crude product is chromatographed over 2 g silica gel, eluting with acetone-hexane (40/60). The fractions containing the title compound are combined and evaporated.

TLC (silica gel): 40% acetone-60% hexane; Rf 0.43.

NMR: Acetone, TMS.

2.47 (s, 3H); 3.67-3.77 (dd, 1H);3.97-4.05 (dd, 1H); 4.20-4.30 (t, 1H); 4,73-4.89 (m, 2H); 7.18 (s, 1H); 7.23 (s, 1H); 7.30-7.39 (t, 1H);7.44-7.52 (t, 1H); 7.54-7.73 (m, 6H); 7.76-7.90 (1m, 3H); 8.14 (s, 1H); 8.39 (d, 1H); 9.75 (s, 2H); 10.48 (s, 1H); 10.92 (s, 1H).

MS: $[M=H]^+$ at 726,728; measured: 726.1748; theory for $C_{38}H_{28}ClF_3N_5O_5$: 726.1731. Other fragment ions: 725, 539, 538, 424, 303, 237, 236, 235, 199, 187, 145.

Example 10E Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-2-methyl]benzo [1,2-b 4,3-b']dipyrrol-4-yl ester, (3,5-dimethylphenyl)-carbamic acid (Cpd #10E).

Following the general procedure of Example 10, 35 mg (0.24 mmol) of 3,5-dimethylphenyl isocyanate and 7 mg (0.072 mmol) triethylamine is added to a 20 mg (0.038 mmol) quantity of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide dissolved in the dark in 1 ml of THF. The reaction is stirred in the dark for 7 days under nitrogen at room temperature. The crude product is

chromatographed over 2 g silica gel, eluting with acetone-hexane (40/60). The fractions containing the title compound are combined and evaporated. Reparified over silica gel eluting with 10% DMF-90% toluene and again using 8% DMF - 92% toluene.

TLC (silica gel): 40% acetone - 60% hexane; Rf 0.49.

NMR: Acetone, TMS.

2.23 (s, 2H); 2.42 (s, 1H); 3.62-3.71 (dd, 1H); 3.93-4.01 (dd, 1H); 4.13-4.23 (t, 1H); 4.65-4.84 (m, 2H); 6.69 (s, 1H); 7.09 (s, 1H); 7.19 (s, 1H); 7.30-7.38 (t, 1H); 7.43-7.51 (t, 1H); 7.54-7.66 (m, 1H); 7.75-7.80 (d, 1H); 8.16 (s, 1H); 8.40 (s, 1H); 9.13 (s, 1H); 9.66 (s, 1H); 10.44 (s, 1H); 11.00 (s, 1H).

MS: $[M-H]^+$ at 686,688; measured: 686.2173; theory for $C_{39}H_{33}ClN_5O_5$: 686.2170. Other fragment ions: 685, 539, 538, 384, 303, 237, 236, 199, 187, 145.

Example 10F Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, (4-chlorophenyl)-carbamic acid (Cpd #10F).

Following the general procedure of Example 10, 35 mg (0.23 mmol) of 4-chlorophenyl isocyanate and 7 mg (0.072 mmol) triethylamine is added to a 20 mg (0.038 mmol) quantity of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]-carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide dissolved in the dark in 1 ml of THF. The reaction is stirred in the dark for 8 days under nitrogen at room temperature. The crude product is chromatographed over 2 g silica gel, eluting with acetone-hexane (40/60). The fractions containing the title compound are combined and evaporated. Rechromatographed over silica gel eluting with 5% DMF - 95% toluene.

TLC (silica gel): 40% acetone - 60% hexane; Rf 0.51.

NMR: Acetone, TMS.

2.47 (s, 3H); 3.65-3.78 (t, 1H); 3.95-4.05 (d, 1H); 4.20-4.30 (t, 1H); 4.71-4.94 (m, 2H); 7.18 (s, 1H); 7.24 (s, 1H); 7.30-7.40 (m, 3H); 7.43-7.53 (t, 1H); 7.53-7.61 (m, 5H); 7.75-7.84 (d, 1H); 7.96 (s, 1H); 8.12 (s, 1H); 8.40 (s, 1H); 9.48 (s, 1H); 9.75 (s, 1H); 10.46 (s, 1H); 10.92 (s, 1H).

MS: $[M-H]^+$ at 692,694. Measured: 692.1469; theory for $C_{37}H_{28}Cl_2N^5O_5$: 692.1467.

Example 10G Preparation of (S)-6-[[5-[(2-benzofuranylcarbonyl)-amino]-1H-indol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, (3,4-difluorophenyl)-carbamic acid (Cpd #10G).

Following the general procedure of Example 10, 35 mg (0.23 mmol) of 3,4-difluorophenyl isocyanate and 7 mg (0.072 mmol) triethylamine is added to a 20 mg (0.38 mmol) quantity of (S)-N-[2-[[1-chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indole-5-yl]-2-benzofurancarboxamide dissolved in the dark in 1 ml of THF. The reaction is stirred in the dark for 10 days under nitrogen at room temperature. The crude product is chromatographed over 2 g silica gel, eluting with DMF-toluene (5/95). The fractions containing the title compound are combined and evaporated. TLC (silica gel): 40% acetone - 60% hexane; Rf 0.55.

NMR: Acetone, TMS.

2.45 (s, 3H); 3.62-3.75 (t, 1H); 3.90-4.03 (d, 1H); 4.15-4.28 (t, 1H); 4.67-4.86 (m, 2H); 7.14 (s, 1H); 7.22 (s, 1H); 7.23-7.41 (m, 2H); 7.42-7.51 (t, 1H); 7.51-7.81 (m, 5H); 7.96 (s, 2H); 8.13 (s, 1H); 8.39 (s, 1H); 9.59 (s, 1H); 9.72 (s, 1H); 10.45 (s, 1H); 10.95 (s, 1H).

MS: $[M-H]^+$ at 694,696; measured: 694.1681; theory for $C_{37}H_{27}ClF_2N_5O_5$: 694.1669.

Example 11 Reaction of (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2-yl]carbonyl]-1H-indol-5-yl]-6-(diethylamino)-2-benzofurancarboxamide with isocyanates

A 0.015 mmol quantity of (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2-yl]carbonyl]-1H-indol-5-yl]-6-(diethylamino)-2-benzofurancarboxamide (U-76073) is dissolved in the dark in 1.0 ml of freshly distilled THF. Two equivalents of the isocyanate and 5 equivalents of triethylamine is added and the reaction mixture stirred from 1 hour to 30 days under nitrogen in the dark at room temperature. The reaction progress is checked by HPLC or TLC. When completed, the crude product is chromatographed over 100 to 1 silica gel, eluting with acetone-hexane. 0.5/1.0 ml fractions are collected and analyzed by TLC. The fractions containing product are combined and evaporated to yield the desired compound.

Example 11A Preparation of (S)-8-(chloromethyl)-6-[[5-[[[6-

(diethylamino)-2-benzofuranyl]carbonyl]amino]-1H-indol-2-yl]carbonyl]-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,5-b']dipyrrol-4-yl ester, 2,2-dimethyl-propanoic acid (Cpd #11A).

A 9 mg (0.016 mmol) quantity of (7bR)-6-diethylamino)-N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl) carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide is dissolved in 150 microL of dry pyridine at 25°C. To this solution is added 6 microL of pivaloyl chloride. After 15 min the reaction is treated with 1 drop of water and then evaporated under vacuum. The residue is placed on top of a 1.5 g silica gel column which is then eluted with acetone-hexane (40/60) followed by pure acetone. The 1 ml fractions (5-28) containing the title compound were combined to give 8 mg of the title compound.

TLC (silica gel): 40% acetone - 60% hexane; Rf 0.44.

NMR: DMSO, TMS.

1.10-1.19 (t, 6H); 1.39 (s, 9H); 2.41 (s, 3H); 3.38-3.49 (q, 4H); 3.69-3.78 (dd, 1H); 3.95-4.04 (dd, 1H); 4.14-4.26 (t, 1H); 4.56-4.64 (m, 1H); 4.67-4.79 (t, 1H); 6.77-6.84 (m, 2H); 7.17 (s, 1H); 7.24 (s, 1H); 7.43-7.50 (d, 1H); 7.51-7.62 (m, 3H); 7.80 (s, 1H); 8.21 (s, 1H); 10.15 (s, 1H); 10.87 (s, 1H); 11.66 (s, 1H).

MS: $[M-H]^+$ at 694,696; $[M]^+$ at 693, 695. Measured: 694.2792; theory for $C_{39}H_{41}Cl_1N_5O_5$: 694.2796. Other fragment ions: 658, 610, 574, 374, 216.

Example 11B Preparation of (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenylamino)carbonyl]oxy]benzo[1,2-b 4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-6-(diethylamino)-2-benzofurancarboxamide (Cpd #11B).

Following the general procedure of Example 11, 4 mg (0.03 mmol) of phenyl isocyanate and 0.7 mg (0.007 mmol) triethylamine is added to a 9 mg (0.015 mmol) quantity of (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2-yl]carbonyl]-1H-indol-5-yl]-6-(diethylamino)-2-benzofurancarboxamide dissolved in the dark in 1 ml of THF. The reaction is stirred in the dark for 36 hr under nitrogen at room temperature. The crude product is chromatographed over 2 g silica gel, eluting with acetone-hexane (40/60) to (80/20). The fractions containing the title compound are combined and evaporated.

TLC (silica gel): 40% acetone - 60% hexane; Rf 0.49.

NMR: DMSO, TMS.

1.09-1.19 (t, 6H); 2.42 (s, 3H); 3.38-3.48 (q, 4H); 3.7-3.8 (t, 1H); 3.96-4.05 (d, 1H); 4.15-4.26 (6, 1H); 4.56-4.66 (m, 1H); 4.71-4.81 (t, 1H); 6.76-6.84 (m, 2H); 7.00-7.10 (t, 1H); 7.15-7.23 (d, 2H); 7.30-7.42 (dd, 2H); 7.43-7.50 (d, 1H); 7.51-7.62 (m, 5H); 7.95 (s, 1H); 8.20 (s, 1H); 10.15 (s, 1H); 10.36 (s, 1H); 11.21 (s, 1H); 11.69 (s, 1H).

MS: $[M-H]^+$ at 729,731; Measured: 729.2587; theory for $C_{41}H_{38}ClN_6O_6$: 729.2592. Other fragment ions: 609,574, 374, 236, 216, 201, 187.

The starting compounds are known or can be readily prepared by known methods. See M.A. Warpehoski, Tet. Lett., 27, 4103 (1986); W. W. Wierenga, J. Am. Chem. Soc., 103, No. 18, 1981; and D.G. Martin, J. Antibiotics 1985, 38, 746. The spirocyclopropylcyclohexadienyl compounds of Formula I can be prepared by the procedures and methods disclosed in copending U.S. Patent Application Serial No. 894,314, filed August 7, 1986, and incorporated herein by reference, and EP Application 0 154 445.

The natural isomers and/or the racemic spirocyclopropylcyclohexadienyl compounds of Formula I can also be prepared by the chemical steps shown in Chart B. The process details of each step are given in the non-limiting procedures which appear as Examples 46-50 of U.S. Patent Application Serial No. 894,314, filed August 7, 1986, and EP Application 0 154 445.

The natural isomers and/or the racemic spirocyclopropylcyclohexadienyl compounds of Formula I can also be prepared by the chemical steps shown in Charts B1 and B2. From the 1,1-dimethylethyl ester of (S)-1-(chloromethyl)-1,6-dihydro-2-Z-5-hydroxy-8-W-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, the natural isomers of Formula I can be prepared in two-step, highly flexible synthesis which allows the conversion of essentially any carboxylic acid to the coupled product as its hydrochloride which then can be converted to the natural spirocyclopropylcyclohexadienyl compound (Formula I) in a single step. The process details of each step are given in the non-limiting procedures which follow. Ms means mesyl; Bzl means benzyl; and Boc means t-butoxy carbonyl (COO-t-butyl).

Chart B1 - Step 1: The starting material 1,2,3,6-tetrahydro-8-methyl-5-(phenylmethoxy)benzo[1,2-b:4,3-b']dipyrrole-1-methanol N-

methanesulfonate is stable, easily handled and described by M.A. Warpehoshki, Tet. Lett., 27, 4103 (1986).

1.0 g (2.6 mmol) of the starting material, in 50 ml freshly distilled THF and 50 ml toluene under nitrogen, is reduced with the dropwise addition and stirring of (5.0 ml, 17 mmol) Red-Al (3.4M solution of bis(2-methoxy-ethoxy)aluminum hydride in toluene). The solution is quickly heated under a flow of nitrogen, allowing the escape of the THF until the internal temperature reaches 85°C. The reaction is allowed to continue at 85°C for 15 minutes and then cooled in an ice bath and carefully treated with 50 ml 15% potassium carbonate. The reaction mixture is then partitioned between water-ethylacetate through which nitrogen is blown. The layers are separated and the aqueous layer reextracted with ethylacetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum. The residual oil is treated with methylene chloride and reevaporated leaving the crude amine 2.

Step 2: The amine product of Step 1 is unstable in air and is therefore stirred at room temperature under nitrogen in 10 ml freshly distilled THF, 0.375 ml triethylamine and 700 mg of 2-(tert-butoxy-carbonyloxyimino)-2-phenylacetonitrile (BOC-ON) for 3.5 days or until TLC shows the reaction to be complete. The reaction mixture is coated on 20g silica gel and placed on top of a 180g silica gel column made up in ethylacetate-hexane (10/90). The column is eluted with 900 ml ethylacetate-hexane (10:90) and 500 ml each of the following ethylacetate-hexane combinations 20:80, 30:70, 40:60; and 50:50. Fractions of 40ml are collected, analyzed by TLC and the fractions (63-73) containing compound 3 collected.

NMR: ($CDCl_3$, TMS, δ) 1.6; 2.3; 3.4-4.4; 5.15; 6.9; 7.2-7.8; 8.5.

Step 3A: 120 mg (0.29 mmol) of the product of step 2, 1,1-dimethylethyl ester of 1-(hydroxymethyl)-1,6-dihydro-8-methyl-5-(phenylmethoxy)-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, is stirred at 0°C under nitrogen in 2 ml pyridine. Syringe in 100 µl mesyl chloride and leave to warm at room temperature for 6 hours. The reaction mixture is cooled to 0°C and a few drops of 5% sodium bisulfate added. After a few minutes the reaction mixture is partitioned between 5% sodium bisulfate and methylene chloride. The layers are separated and the aqueous layer reextracted with methylene

chloride. The organic layers are washed with water, dried over sodium sulfate, combined and evaporated under vacuum to yield the crude product 6.

NMR: ($CDCl_3$, TMS, δ) 1.6; 2,4; 2.8; 3.6-4.6; 5.1; 6.9; 7.2-7.7; 8.4.

Step 3B: 242 mg (0.59 mM) of the product of step 2, 1,1-dimethylethyl ester of 1-(hydroxymethyl)-1,6-dihydro-8-methyl-5-(phenylmethoxy)-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, is dissolved in distilled THF (2.4 ml) and absolute ethanol (25 ml). The compound is hydrogenalized over 10% palladium on carbon (192 mg) at 42 PSI for 50 minutes. The reaction is filtered through diatomaceous earth, washing with absolute ethanol. Evaporation yields compound 4, 1,1-dimethylethyl ester of 1-(hydroxymethyl)-1,6-dihydro-8-methyl-5-hydroxy-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid.

NMR: (Acetone-d_6, TMS, δ) 1.55; 2.39; 2.98-4.07; 4.07-4.48; 7.05; 7.40; 8.81; 9.79.

TLC (Silica gel GF): R_f= 0.60 in ethyl acetate-hexane (50/50).

Step 4A: 200mg (0.29 mmol max) of the product of step 3A, 1,1-dimethylethyl ester of 1-(methanesulfonyloxymethyl)-1,6-dihydro-8-methyl-5-(phenylmethoxy)-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, the crude mesylate, is stirred under nitrogen at 80°C in 3 ml DMF and 40 mg lithium chloride for 25 minutes, when TLC shows the reaction to be complete. The reaction mixture is cooled to room temperature, and partitioned between methylene chloride and water. The layers are separated and the aqueous layer reextracted with methylene chloride. The organic layers are combined, dried over sodium sulfate and evaporated under high vacuum. The crude product is chromatographed over 10g silica gel, eluting with ethyl acetate-hexane (20:80). Fractions of 5 ml are collected and the product found by TLC in fractions 7-17, which upon combining and evaporating yield compound 7, 1,1-dimethylethyl ester of 1-(chloromethyl)-1,6-dihydro-8-methyl-5-(phenylmethoxy)-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid.

MS: $[M+H]^+$ at 427,429; $[M]^+$ at 426,428. Measured: 426.1721; theory for $C_{24}H_{27}ClN_2O_3$: 426.1710.

NMR: ($CDCl_3$, TMS, δ) 1.6; 2.4; 3.2-4.5; 5.2; 7.0; 7.3-7.7; 8.3.

Step 4B: A 145 mg quantity (0.455 mM) of the diol 4, 1,1-

dimethylethyl ester of 1-(hydroxymethyl)-1,6-dihydro-8-methyl-5-hydroxy-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, is treated with freshly distilled THF (7.4ml), triphenylphosphine (189.5 mg, 0.722 mM), and diethylazodicarboxylate (110 µl, 0.700 mM) under nitrogen. The reaction is stirred 80 minutes at room temperature and adsorbed onto 3g of silica gel and chromatographed on a 27g silica gel column in distilled THF-hexane (45/55). Fifteen ml fractions are collected. The product fractions are collected, evaporated and triturated with ethyl acetate to give compound 5, 1,1-dimethylethyl eater of 4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo(3,2-e)indol-2(1H)-carboxylic acid.

NMR: ($CDCl_3$ + CD_3OD, TMS, δ) 1.08-1.42; 1.58; 1.84-2.17; 2.80-3.14; 3.29-3.48; 6.73; 6.93.

TLC (Silica Gel GF): R_f=0.36 in ethyl acetate-hexane (60/40), Rf=0.5 in THF-hexane (50/50).

Step 5A: A 110 mg quantity (0.26 mM) of the product of Step 4A, 1,1-dimethylethyl ester of 1-(chloromethyl)-1,6-dihydro-8-methyl-5-(phenylmethoxy)-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, is stirred at room temperature under nitrogen in 2 ml freshly distilled THF and 2 ml methanol. 120 mg 10% Pd/C (palladium on charcoal) and 130 mg ammonium formate is added. After TLC shows the reaction mixture to be complete, the reaction mixture is filtered, and the solid washed with freshly distilled THF. The combined filtrate and wash is partitioned between ethyl acetate and brine (saturated aqueous sodium chloride solution), the layers separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated to yield (BOC)CPI hydrochloride, 1,1-dimethylethyl ester of 1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methyl-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid.

NMR: ($CDCl_3$, d_6-acetone, TMS, δ) 1.6; 2.4; 3.3-4.4; 7.1; 7.4; 8.9; 9.7

MS: measured 336.1230; theory for $C_{17}H_{21}ClN_2O_3$ 336.1241

Chart B2 - Step 1: 16.1 mg (0.048 mmol) of (BOC)CPI hydrochloride, 1,1-dimethylethyl ester of (S)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methyl-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid is dissolved in ethyl acetate under an inert atmosphere (nitrogen), treated with 2 ml of an HCl-saturated ethyl

acetate solution and the reaction run at room temperature for 40 minutes. The reaction mixture is evaporated to dryness under vacuum, then the flask recharged with nitrogen. The solid is dissolved in methylene chloride and evaporated again to remove traces of acid. The crude amine salt is used immediately in the next step.

Step 2: The crude amine salt of step 1A is stirred in dry dimethylformamide (0.95 ml) with 25.2 mg (0.048 mmol) of 7-[[7-(aminocarbonyl-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo-[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, (PDE1 dimer, see DG Martin, J Antibiotics, 1985, 38, 746) and 9.4 mg (0.049 mmol) 1-ethyl-3(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC). The reaction is maintained under nitrogen at room temperature for two hours, diluted with water and centrifuged. The liquid is removed and the solid washed with water. After drying under vacuum overnight, the solid is absorbed onto 0.76 g of silica gel from DMF and placed on a 5 g silica column and eluted with DMF-acetone-methylene chloride (8-17-75). Fractions of 3 ml are collected and the desired product isolated from the fractions (8-29).

NMR: (DMSO-d7, TMS, δ) 1.24; 2.36; 3.27; 3.58; 3.83; 3.90; 3.83-4.12; 4.41-4.79; 6.88-7.10; 7.67; 7.55; 9.80; 10.72; 10.93; 11.37.

Step 3: 10 mg (0.013mmol) of the product of step 2A having the S stereochemistry is stirred under nitrogen with 4 ml of acetonitrile, 1 ml water, and 1 ml triethylamine for 25 minutes. The reaction mixture is partitioned between ethyl acetate and water. The aqueous layer is extracted with additional ethyl acetate and the combined organic layer are washed with water, dried over sodium sulfate and evaporated to yield the product, natural CC-1065.

NMR (DMSO-d6, TMS, δ): 0.68-1.35; 1.47; 2.005; 3.823; 3.863; 4.04; 4.37; 4.70; 6.45; 6.8-7.2; 11.06; 11.38; 11.54.

Following the procedures of Steps 1,2 and 3 (Chart B2) and starting with 1,1-dimethylethyl ester of (R)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methyl-benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxylic acid, ent-CC-1065 is prepared. CD in DMF: nm(molar-ellipticity) 330 (+32,000), 290(-42,000).

All the compounds of the subject invention have UV absorption in the range of 200 nm to 380 nm. Thus, novel compounds of the subject

invention (Formula I') are useful as UV absorbents in technical and industrial areas, as follows:

(a) textile materials, for example, wool, silk, cotton, hemp, flax, linen and the like;

(b) natural or synthetic resins.

Depending on the nature of the material to be treated, the requirements with regard to the degree of activity and durability, and other factors, the proportion of the light screening agent to be incorporated in the material may vary within fairly wide limits, for example, from about 0.01% to about 10%, and, advantageously, 0.1% to 2% of the weight of the material which is to be directly protected against the action of UV rays.

The compounds of Formula I' are particularly useful as antitumor agents. Examples of compounds of Formula I' demonstrate antitumor activity in P388 leukemic mice, and also show significant activity in the L1210 leukemia and B16 melanemia murine test systems. These murine test systems are predictive for clinically useful human antitumor agents (see, for example, A. Geldin et al, European J. Cancer, Vol. 17, pp 129-142, 1981; J.M Vendetti, Cancer Treatment Reports, Vol. 67, pp. 767-772, 1983; and J.M. Vendetti et al, Advances in Pharmacology and Chemotherapy, Vol. 20, pp. 1-20, 1984), and, therefore, the compounds of the subject invention (Formula I') will be useful in the control and treatment of susceptible neoplastic (cancer) diseases in humans when given, for example, intravenously in doses of 0.001 to about 10 mg/kg of body weight per day, the exact dose depending on the age, weight, and condition of the patient, and on the frequency of administration.

The compounds of Formula I' are advantageous over their cyclized counterpart. (Formula I) and its ring opened phenol synthetic precursors (Formula I' wherein Y = H and X = Br, Cl, I, or OSO_2CH_3) because of improved solubility, increased stability, improved half life in the animal or human, improved bodily distribution, and improved therapeutic index over the cyclized counterparts and their alcohol synthetic precursors. The compounds of Formula I' are effective when administered intravenously (IV) in fluid solutions by bolus injection or by infusion. The preferred doses are 5 microgram/kg to 1000 microgram/kg by bolus injection and 0.002 to 200 microgram/kg/min by infusion. The exact dose will vary depending on

the particular compound as well as the age, weight, route of administration, and physical condition of the patient, and on the frequency of administration.

Illustrative in vivo testing data on the compounds of Formula I' and comparison with their spirocyclopropyl analogs (Formula I) and chlorophenol analogs are presented in Table 1. The structures of the various compounds of Formula I' are presented in Table 2 and their spirocyclopropropylcyclohexadienyl and chlorophenol analogs are presented in Table 3.

The compounds of Formula I' show several favorable biological effects. The compounds of Formula I' generally show activity over an additional dose level compared with the corresponding compounds of Formula I (data not shown). In addition, the compounds of Formula I' often show superior activity. For example see Table 1, comparison of entry 1 with entries 26 and 29 shows that the acetate Cpd #1 given IV is superior vs IP administered L1210 leukemia when compared with its SCPCH precursor U-71184 and its chlorophenol precursor U-73903. Similarly, the CC-1065 derived decanoate Cpd #3 (entry 16) and hexanoate Cpd #5 (entry 25) when administered IP on days 1, 5, and 9 show superior activity to CC-1065 (U-56314 entry 36) also administered by the same dose schedule. Although a direct comparison is not available in all cases, the table strongly indicates a superiority of the prodrugs by the oral route of administration. Thus, Cpd #1 (entry 3) given orally on days 1-5 has superior activity vs IP P388 compared to U-71184 (entry 28) and U-73903 (entry 31) given by the same route and schedule. While there is no direct comparison for the excellent oral activity of Cpd #2A (entry 7) or Cpd #2E (entry 13), it should be noted that generally L1210 is a more difficult system than the P388 system and that vs the various leukemias U-71184 has generally shown slightly superior activity to U-73975. Thus, it is quite impressive that oral Cpd #2A (entry 7) and oral Cpd #2E (entry 13) show superior activity vs L1210 compared with the oral activity of Cpd #1 vs L1210 (entry 2) and vs P388 (entry 3). The activity difference is even greater when compared with the oral activity of U-71184 and U-73903 vs P388 (entries 28 and 31).

The results set forth in Tables 1 and 4 were obtained using standard well known procedures (In Vivo Cancer, Models, NIH Publication No. 84-2635, 1984).

T/C refers to median life span of treated mice divided by median life span of control mice times 100.

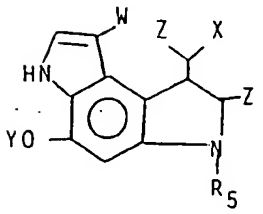
The compounds of formula I', where X is halogen and Z is hydrogen, are useful as antibacterial agents. These compounds are useful to control the proliferation of susceptible microbes in various environments using standard microbiological techniques. Such environments include laboratory benches in a microbiological laboratory which can be cleansed with a formulation of compounds of formula I', where X is halogen and Z is hydrogen; dental utensils contaminated with S. aureus, and the like.

Relative to the compounds claimed in this case, the O-protected compounds described in EP 154445 are significantly less biologically effective, particularly in terms of antitumor potency. The O-protected compounds of Formula II in EP 154445 are important as synthetic intermediates necessary to make the biologically active compounds of EP 154445 (compounds of Formula I or of Formula II when R_1 is H). The O-protecting groups in EP 154445 are chemically stable and only removable under specific chemical conditions. More importantly, the O-protected compounds of EP 154445 are not readily cleaved under physiological conditions to the active species and are therefore much less effective than the compounds of this case. In general the groups on the phenol in the compounds of this case are too labile to function as good protecting groups since they would be cleaved prematurely (such as at the RedAl step (Chart B1, step 1) in the synthesis). In accord with this, the groups on the phenol in this case appear to be labile even to physiological conditions, thus being pro-drugs which can be converted ultimately to the highly biologically active compounds of Formula I of EP 154445.

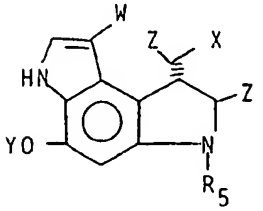
For a specific example, the O-benzylated product of Example 48, step 5 at page 42 (and step 5, chart IV at page 87) of U.S. Patent Application Serial No. 894,314, filed August 7, 1986. (See also, EP Application 0 154 445) has less than 1/10 the potency of any of the corresponding O-acylated compounds (2A through 2G in Table 2).

Similarly, U-69815 (page 54 of U.S. Patent Application Serial No. 894,314, filed August 7, 1986, and EP Application 0 154 445) has less than 1/20 the potency of the corresponding O-acetylated compound (compound 1 of Table 2).

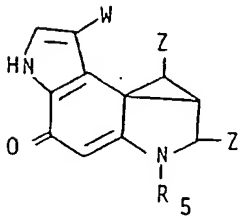
GENERAL FORMULAE CHART



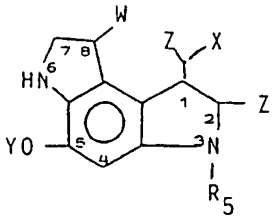
I'



I'a

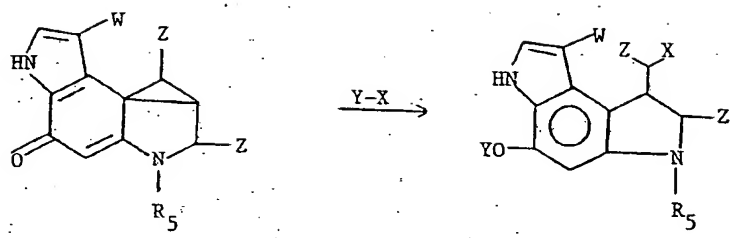


I



B'

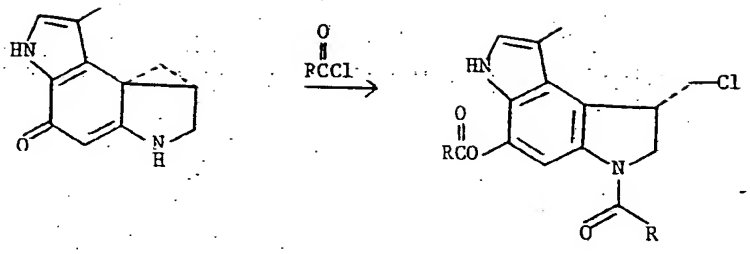
CHART A



I I'

CHART A'

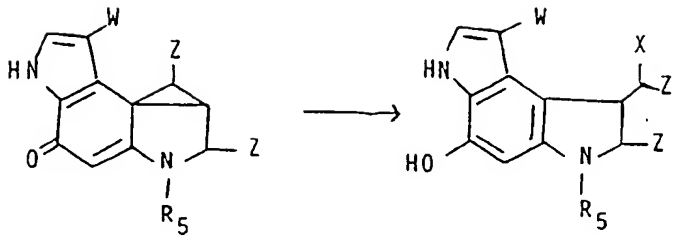
CHART A''



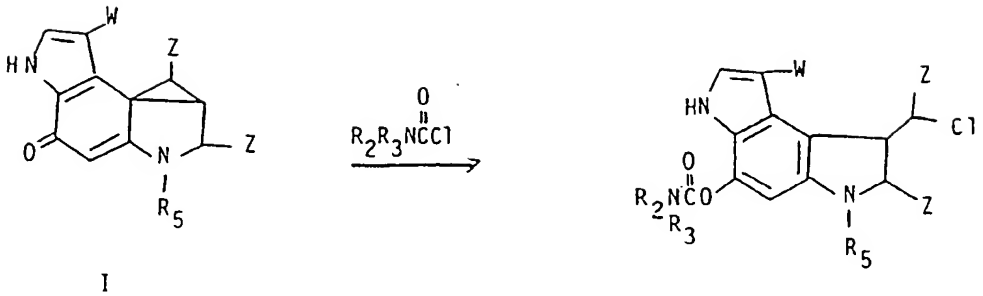
Example 7 R = n-C_5H_{11} = n-pentyl

Example 8 R =  Cl = 4-chlorophenyl

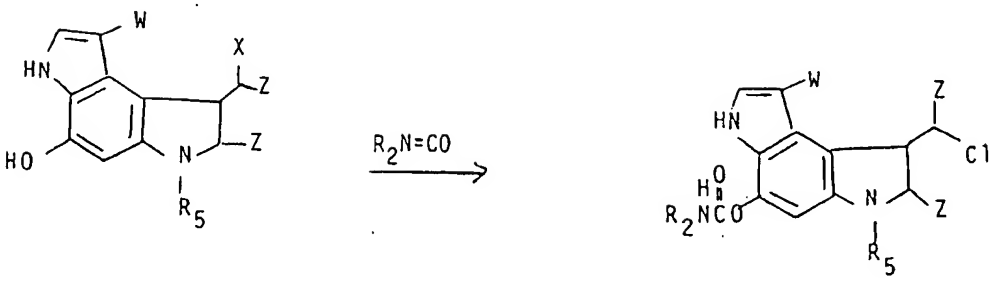
CHART A'''



I II



I



II

CHART B

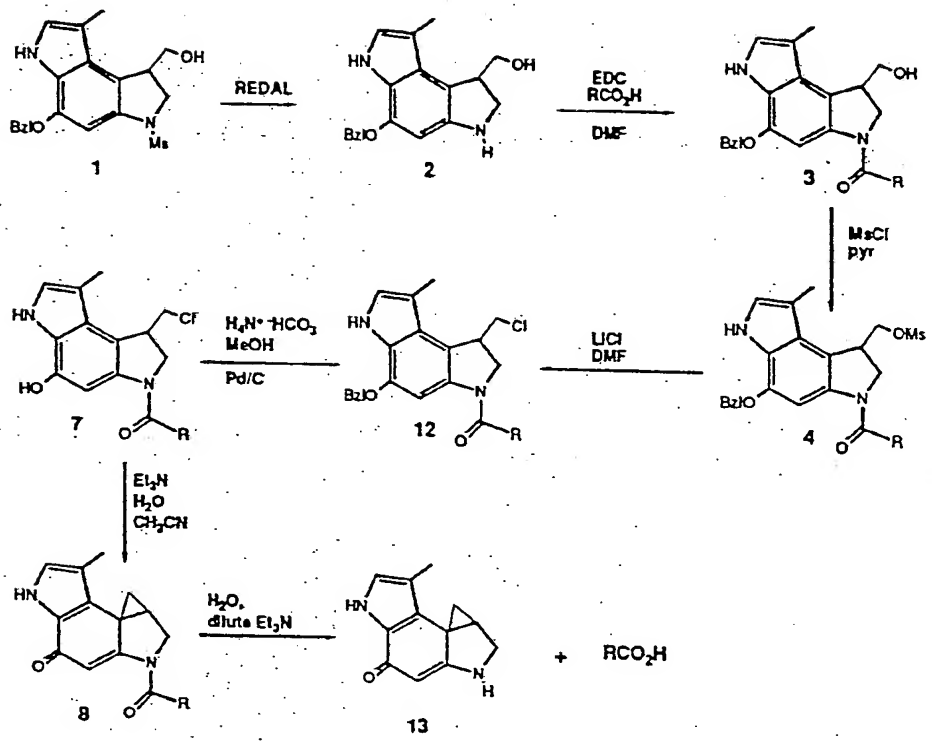
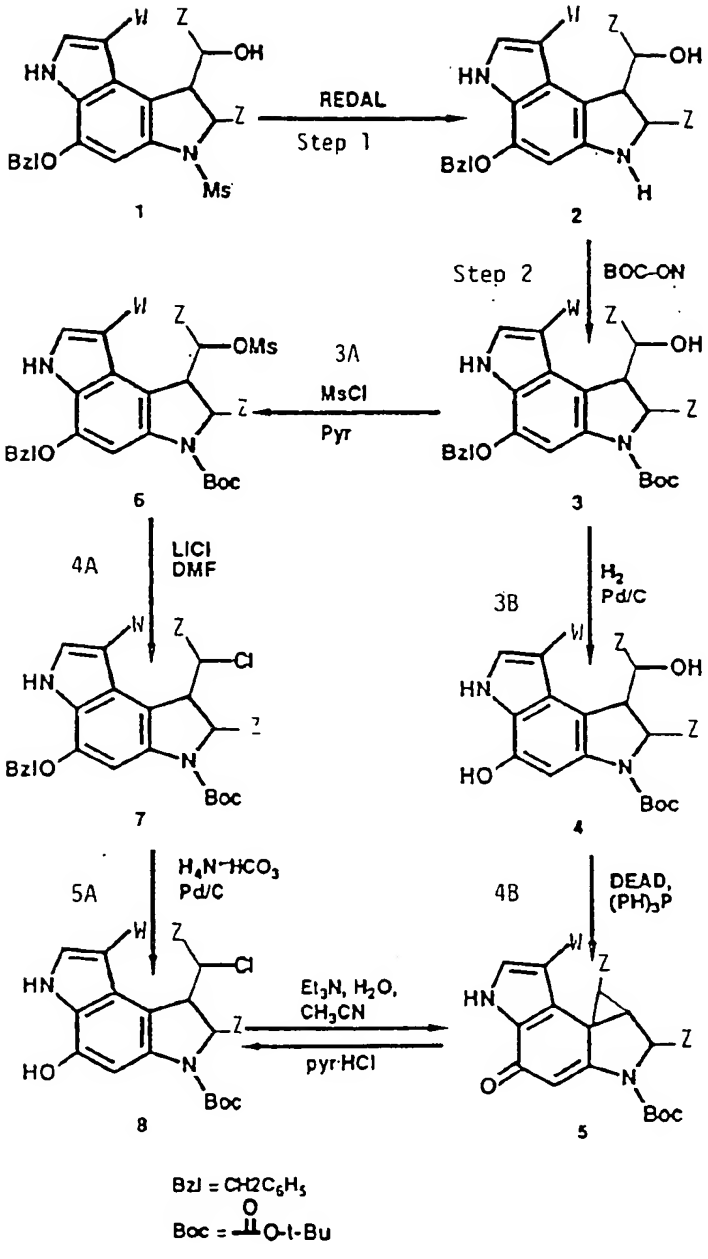

REDAL
EDC
RCO2H
DMF
MsCl
pyr
H4N+ HCO3
MeOH
Pd/C
LiCl
DMF
Et3N
H2O
CH3CN
H2O,
dilute Et3N
+ RCO2H

CHART B1



Bzl = $CH_2C_6H_5$

Boc = O-t-Bu

CHART B2

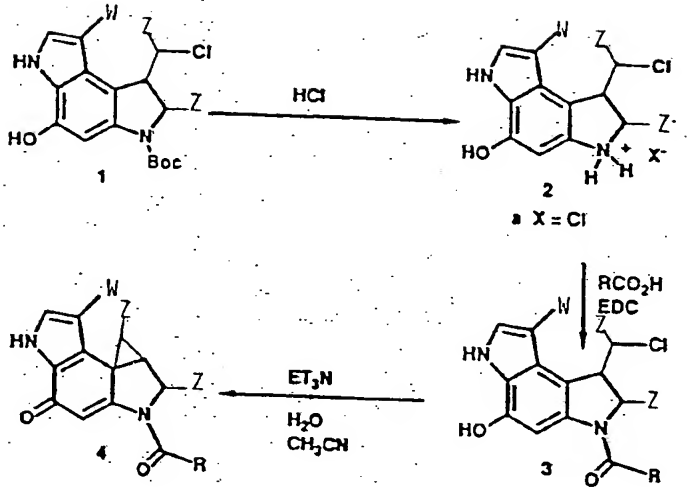
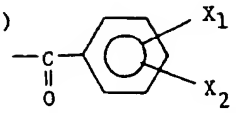


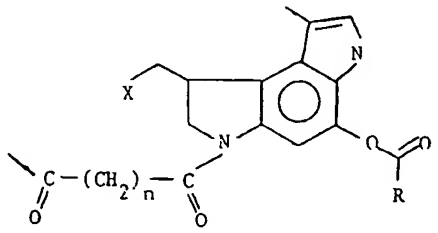
CHART C

(i) $-C(O)-R_6$ where R_6 is H, -alkyl (C_1-C_{20}), $-CCl_3$, CF_3, or NH_2,

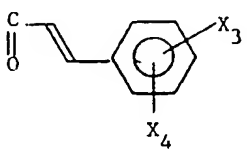
(ii)  where X_1 and/or X_2 is H, CH_3, OH, OCH_3, NO_2, NH_2, (NHNHAc) $NHNHC(O)CH_3$, (NHBz) $NHC(O)C_6H_5$, or halogen;

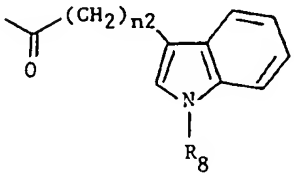
(iii) acyl derivatives ($-C(O)-CHNH_2-R_7$) of the 20 natural amino acids where R7 is the amino acid residue of glycine, alanine, valine, isoleucine, leucine, serine, threonine, aspartic acid, glutamic acid, lysine, arginine, asparagine, glutamine, cysteine, methionine, tryptophan, phenylalanine, tyrosine and histidine or proline; and their common salts selected from Na^+, K^+, NH_4^+, HCl, H_3PO_4 and (HOAc) $HOC(O)CH_3$;

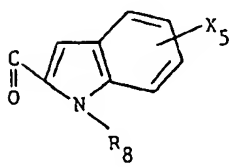
(iv) $-C(O)-CH_2CH_2-CO(C)^- M^+$ is Na, K, NH_4, or $N(CH_3)_4$;

(v) 

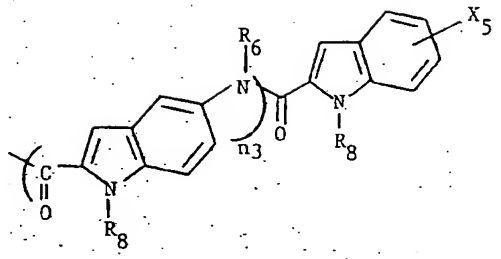
(dimer) wherein nl = 2-12;

(vi)  where X_3 and/or X_4 = H, OH, OCH_3;

(vii)  where n2 = 1-3; and R_8 is H, CH_3 or C_2H_5;

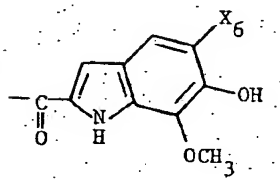
(viii)  where X_5 = H, OH, OCH_3, NO_2, NH_2, (NHAc) $NHC(O)CH_3$, $NHC(O)NH_2$; (NHBz) $NHC(O)C_6H_5$; NH-CN; and R_8 has the meaning defined above;

(ix)



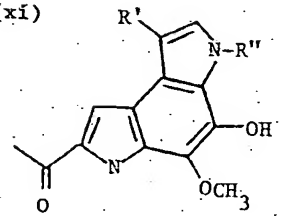
where n3 = 1, 2, or 3; and R_8, R_6 and X_5, have the meanings defined above;

(x)



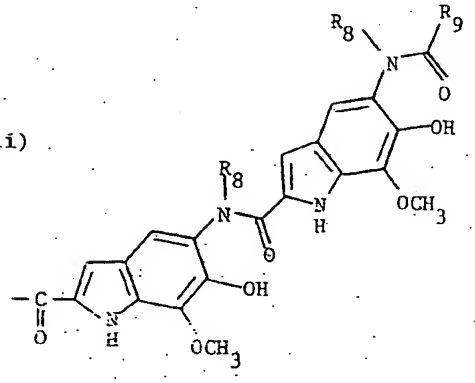
where X_6 = H, NO_2, NH_2, NHAc, $NHC(O)NH_2$;

(xi)

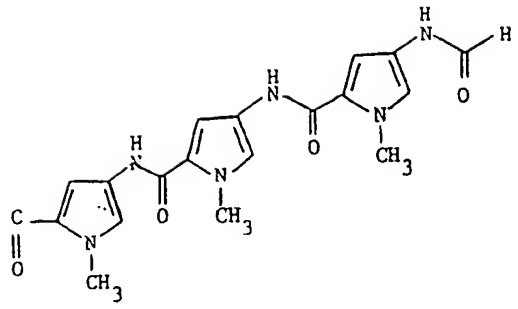


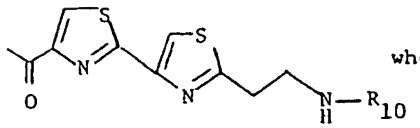
wherein R' is H or CH_3S- and R" is $NH_2(C)O$- or $CH_3C(O)$-;

(xii)



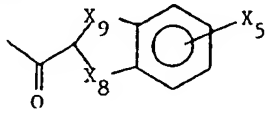
where R_8 has the meanings defined above, and R9 is $-CH_3$ or $-NH_2$;

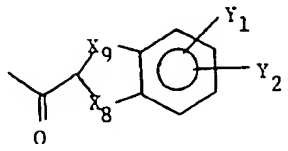
(xiii) 

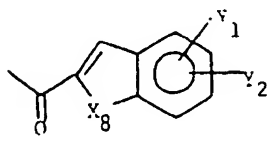
(xiv)  where R_{10} - CCH_3, CPh, H·HCl;

(xv) $-C(O)-(-R_{11}-)-C(O)-X_7-(-CH_2CH_2-X_7)n4-H$ where R_{11} - CH_2CH_2, CH=CH; and X_7 - O, NH, and n4 - 1-4, and the HCl and MeI salts for X_7 - NH;

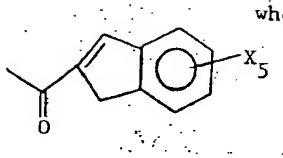
(xvi) $-C(O)-(-R_{11}-)-C(O)-X_7-(-CH_2CH_2-X_7)n4-C(O)-(-R_{11}-)-C(O)-$ (dimer) where R_7 and R_{11} and n_4 have the meanings defined above;

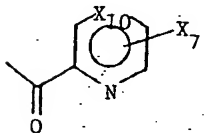
(xvii)  where X_8 is -O-, -S-, NH; X_9 is -CH= or -N=; and X_5 has the meaning defined above;

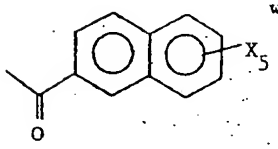
(xviia)  where X_9 and X_8 have the meanings defined above; and Y_1 and/or Y_2 - H, halo, C_1-C_4-alkyl, C_1-C_3-alkoxy, C_2-C_6-dialkylamino, nitro, amino-carbonylalkyl(C_1-C_{10}), hydroxy, amino ($-NH_2$), $-NHCONH_2$, -NHAc ($NHCOCH_3$) or-NHBz ($-NHC(O)C_6H_5$);

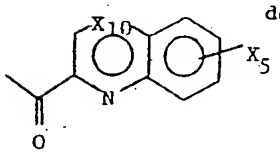
(xviib)  where X_8, Y_1 and Y_2 have the meanings

defined above;

(xviii)  where X_5 has the meaning defined above;

(xix)  where X_{10} is -CH= or -N= and X_7 is SH, NH_2, OH, H, or NHAc;

(xx)  where X_5 has the meaning defined above;

(xxi)  where X_5 and X_{10} have the meanings defined above; and

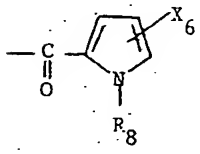
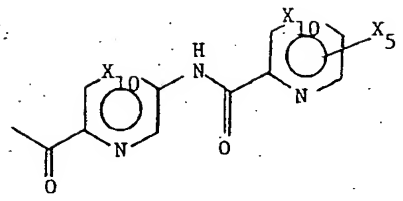
(xxii)  where X_6 and R_8 have the meanings defined above.

CHART D

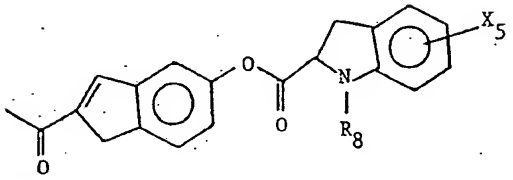
	ii + ii	ii + vi
	ii + viii	ii + ix
5	ii + xvii	ii + xviii
	ii + xix	ii + xx
	ii + xxi	ii + xxii
	vi + vi	vi + viii
	vi + ix	vi + x
10	vi + xvii	vi + xviii
	vi + xix	vi + xx
	vi + xxi	vi + xxii
	viii + viii	viii + ix
	viii + xviib	viii + xviia
15	viii + x	xviii + xvii
	viii + xviii	viii + xix
	viii + xx	viii + xxi
	viii + xxii	ix + ix
	ix + x	ix + xvii
20	ix + xx	ix + xxi
	ix + xxii	x + x
	x + xvii	x + xviii
	x + xix	x + xx
	x + xxi	x + xxii
25	xvii + xvii	xvii + xviii
	xviia + xviia	xvii + xviia
	xvii + xix	xvii + xx
	xvii + xxi	xvii + xxii
	xviii + xviii	xviii + xvii
30	xviii + xix	xviii + xx
	xviii + xxi	xviii + xxii
	xix + xix	xix + xx
	xix + xxi	xix + xxii
	xx + xx	xx + xxi
35	xx + xxii	xxi + xxi
	xxi + xxii	xxii + xxii

CHART E

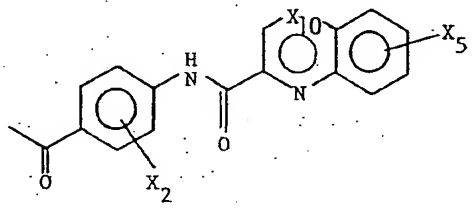
R_5 = xix + xix =



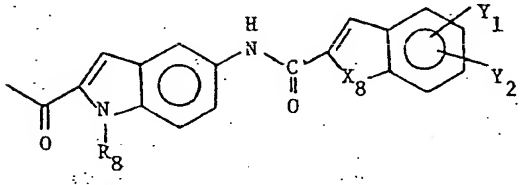
R_5 = xviii + viii =



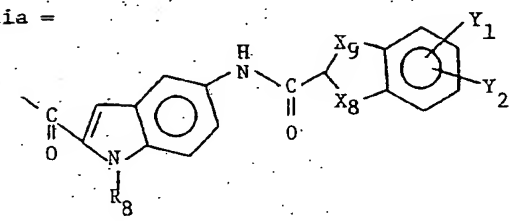
R_5 = ii + xxi =



R_5 = viii + xviib =



R_5 = viii + xviia =



R_5 = viii + viii =

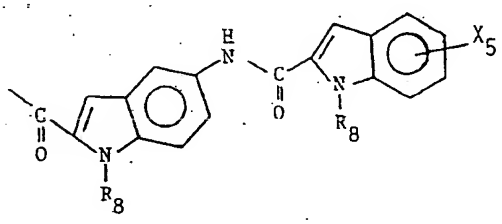


TABLE 1

Comparison of the in vivo Biological Activity of Compounds of Formula I' and I.

ENTRY #	CPD#	TEST	RT ADMIN TUM/DRUG	DAYS OF DOS	MG/KG	T/C	30 DAY SURVIV
Prodrugs							
1	1	L1210	IPIV	1	0.20	*	3/6
2	1	L1210	IP-ORAL	1,5,9	0.60	128	-
3	1	P388	IP-ORAL	1-5	0.16	120	-
4	1	P388	IPIV	1	0.20	*	4/6
5	2A	L1210	IPIV	1	0.20	200	-
6	2A	L1210	IPIV	1	0.40	181	-
7	2A	L1210	IP-ORAL	1,5,9	0.60	175	-
8	2A	P388	IPIV	1	0.20	263	2/6
9	2B	L1210	IPIV	1	0.20	188	-
10	2C	L1210	IPIV	1	0.20	200	1/6
11	2D	L1210	IPIV	1	0.20	194	-
12	2E	L1210	IPIV	1	0.20	182	-
13	2E	L1210	IP-ORAL	1	0.20	150	-
14	2F	L1210	IPIV	1	0.20	188	-
15	3	L1210	IPIV	1	0.20	257	
16	3	P388	IPIP	1,5,9	0.05	*	4/6
17	3	B16	IPIV	1	0.10	175	-
18	3	B16	IPIV	1	0.20	190	-
19	3	LLUNG	SCIV	1	0.10	142	-
20	3	LLUNG	SCIV	1	0.05	102	-
21	6	L1210	IPIV	1	0.40	200	-
22	2G	L1210	IPIV	1	0.10	171	-
23	4	L1210	IPIV	1	0.20	243	-
24	4	B16	IPIV	1	0.40	181	-
25	5	P388	IPIP	1,5,9	0.05	255	2/6
U-71184 and its chlorophenol							
26	71184	L1210	IPIV	1	0.10	158-200	0/6-1/6
27	71184	P388	IPIV	1	0.05-0.20	191-263	0/6-4/6
28	71184	P388	IP-ORAL	1-5	0.08	100	-
29	73903	L1210	IPIV	1	0.20	200-213	0/6-1/6
30	73903	P388	IPIV	1	0.20	242	1/6-3/6
31	73903	P388	IP-ORAL	1-5	0.16	105	-

* These are the most active compounds. However, with 3 or more 30-day survivors a median day of death for a 6 animal group cannot be calculated.

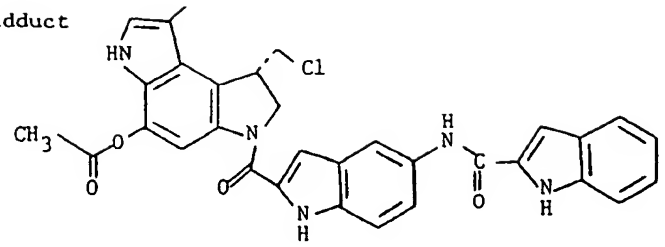
TABLE 1 (cont)

ENTRY #	U#	TEST	RT ADMIN TUM/DRUG	DAYS OF DOS	MG/KG	T/C	30 DAY SURVIV
U-73975 and its chlorophenol							
32	73975	L1210	IPIV	1	0.05-0.10	163-243	0/6-2/6
33	73975	P388	IPIV	1	0.05-0.10	200-230	0/6-2/6
34	73896	L1210	IPIV	1	0.05-0.20	163-213	0/6-2/6
35	73896	P388	IPIV	1	0.10-0.20	232-240	0/6-1/6
CC-1065							
36	56314	P388	IPIP	1,5,9	0.01-0.05	123-168	

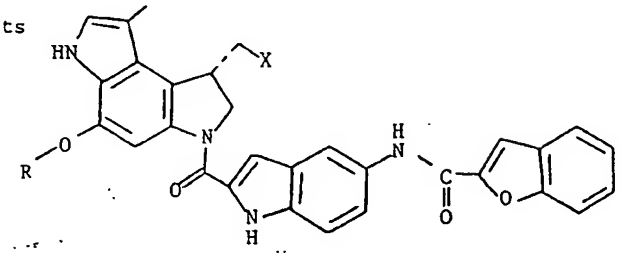
TABLE 2

1. U-71184 adduct

Cpd #1



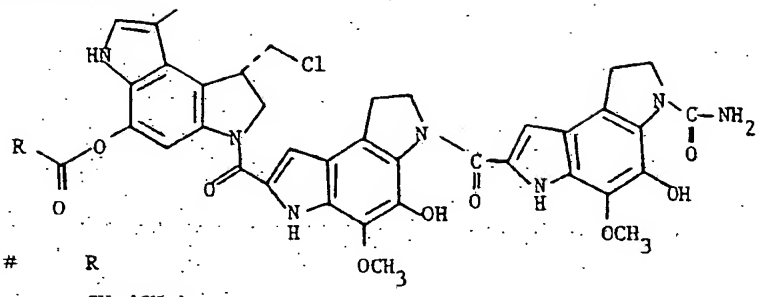
2. U-73975 adducts



Cpd #	X	R
2A	Cl	CH_3CO
2B	Cl	$CH_3(CH_2)_4CO$
2C	Cl	C_6H_5CO
2D	Cl	$CH_3(CH_2)_{12}CO$
2E	Cl	$CH_3(CH_2)_8CO$
2F	Cl	$CH_3(CH_2)_{10}CO$
6	N_3	H
2G	Br	C_6H_5CO
10A	Cl	C_6H_5NHCO-
10B	Cl	$CH_3(CH_2)_3NHCO$-
10C	Cl	$(CH_3)_3CCO$-
10D	Cl	4-$(CF_3)_2C_6H_4NHCO$-
10E	Cl	3,5-$(CH_3)_2C_6H_3NHCO$-
10F	Cl	4-ClC_6H_4NHCO-
10G	Cl	3,4-$(F)_2C_6H_3NHCO$-

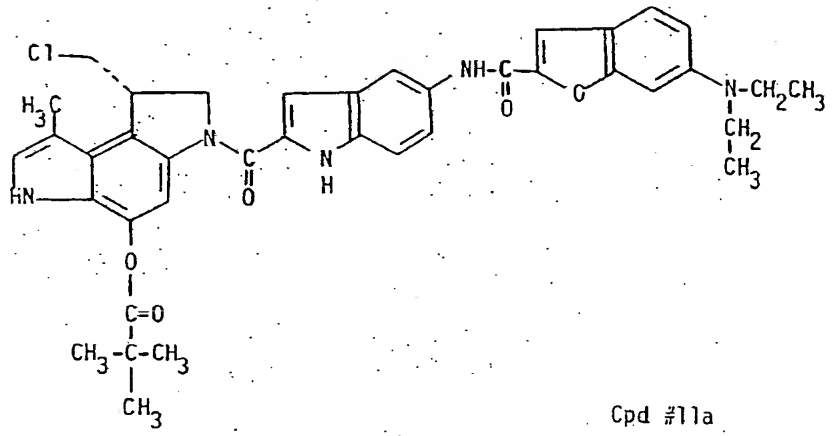
TABLE 2 (Continued)

3. CC-1065 adducts

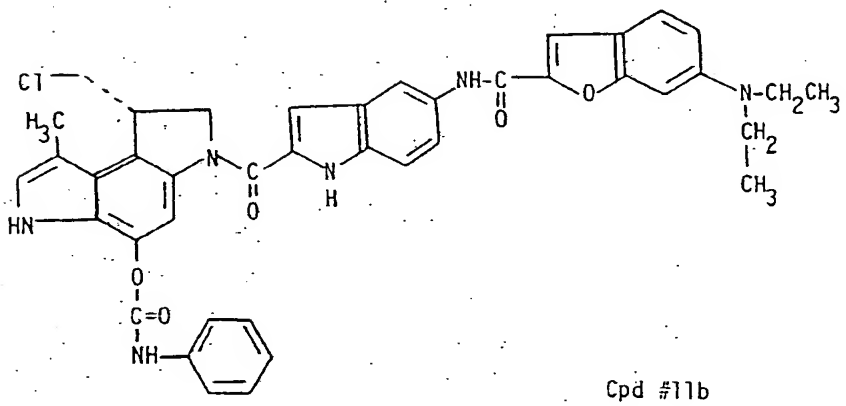


Cpd #	R
3	$CH_3(CH_2)_8$
4	$CH_3(CH_2)_{12}$
5	$CH_3(CH_2)_4$

4. U-76074 adducts

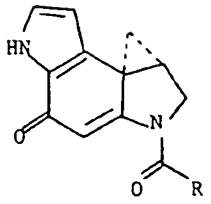


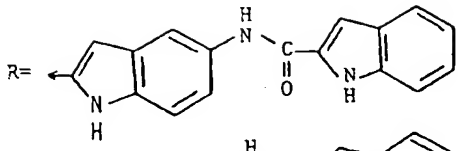
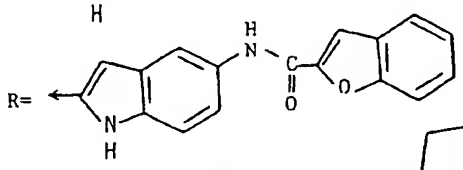
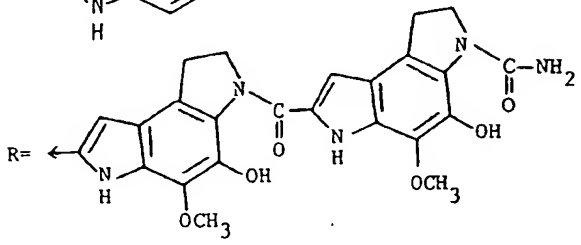
Cpd #11a

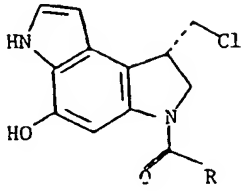


Cpd #11b

TABLE 3



Cpd # U #	R=
U-71184	
U-73975	
U-56314	



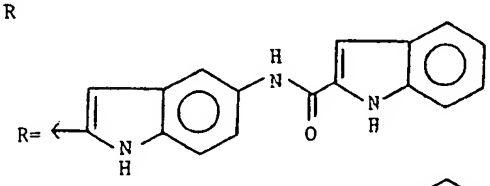
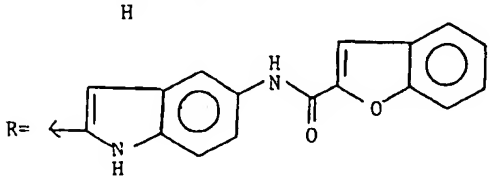
U-73903	
U-73896	

TABLE 3 (Continued)

U-76073

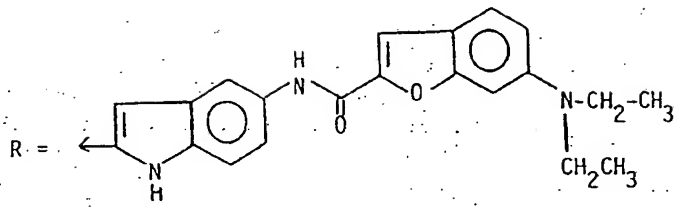
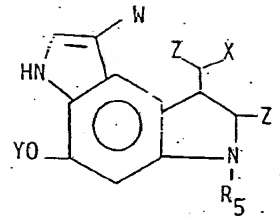


TABLE 4

U#	Test	Rt Admin Tum/Drug	Days of Dos.	mg/ kg	Microm/ kg	T/C	Cures
10A	B16	IPIV	1	0.20	0.30	163	--
10A	B16	IPIV	1	0.20	0.30	154	--
10A	L1210	IPIV	1	0.20	0.30	250	1/6
10A	L1210	IPIV	1	0.20	0.30	213	--
10B	LLUNG	IVIP	1,5,9	0.10	0.16	271	2/8
10B	LLUNG	IVIV	1	0.20	0.31	*	4/8
10B	L1210	IPIV	1	0.20	0.31	200	--
10C	L1210	IPIV	1	0.10	0.16	200	--
10D	L1210	IPIV	1	0.30	0.41	188	--
10E	L1210	IPIV	1	0.30	0.44	200	--
10F	L1210	IPIV	1	0.40	0.58	213	--
10F	L1210	IPIV	1	0.40	0.58	213	--
11A	L1210	IPIV	1	0.40		225	2/6
11A	B16	IPIV	1	0.5		175	--
11B	L1210	IPIV	1	0.6		213	3/6
11B	B16	IPIV	1	0.5		175	--

CLAIMS

1. A compound of formula I'



I'

wherein W is selected from C_1-C_5 alkyl, phenyl or hydrogen;

wherein X is selected from azido, a halogen atom, cyanate, thiocyanate, isocyanate, thioisocyanate, phosphate diester ($-PO(OR)_2$), phosphonyl ($-O-PO_2R$), thiophosphonyl (-O-PSOR), sulfinyl (-O-SOR) or sulfonyl ($-O-SO_2R$);

wherein Y is selected from hydrogen, -C(O)R, -C(S)R, $-C(O)OR_1$, $-S(O)_2R_1$, $-C(O)NR_2R_3$, $-C(S)NR_2R_3$, or $-C(O)NHSO_2R_4$; with the proviso that when X is a bromo, chloro or iodo atom, Y is not hydrogen;

wherein Z is selected from the group consisting of C_1-C_5 alkyl, phenyl or hydrogen;

wherein R is selected from the group consisting of C_1-C_{20} alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, trifluromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_1 is selected from C_1-C_{20} alkyl or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

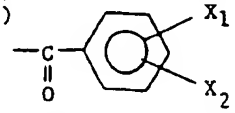
wherein R_2 and R_3, being the same or different, are selected from hydrogen, C_1-C_{20} alkyl, or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; with the proviso that both R_2 and R_3 can not be phenyl or substituted phenyl;

wherein R_4 is selected from C_1-C_{10} alkyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo,

trifluromethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_5 is a carbonyl acyl group selected from the group consisting of

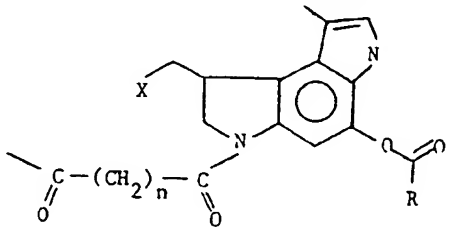
(i) -C(O)-R_6 where R_6 is H, -alkyl (C_1-C_{20}), -CCl_3, CF_3, or NH_2,

(ii)  where X_1 and/or X_2 is H, CH_3, OH, OCH_3, NO_2, NH_2, (NHNHAc) $NHNHC(O)CH_3$, (NHBz) $NHC(O)C_6H_5$, or halogen;

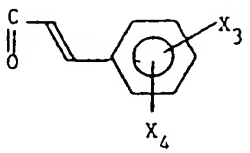
(iii) acyl derivatives (-C(O)-$CHNH_2$-R_7) of the 20 natural amino acids where R7 is the amino acid residue of glycine, alanine, valine, isoleucine, leucine, serine, threonine, aspartic acid, glutamic acid, lysine, arginine, asparagine, glutamine, cysteine, methionine, tryptophan, phenylalanine, tyrosine and histidine or proline; and their common salts selected from Na^+, K^+, NH_4^+, HCl, H_3PO_4 and (HOAc) $HOC(O)CH_3$;

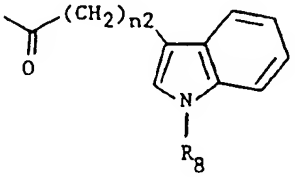
(iv) -C(O)-CH_2CH_2-$CO(C)^-$ M^+ is Na, K, NH_4, or $N(CH_3)_4$;

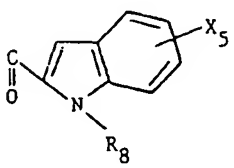
(v)



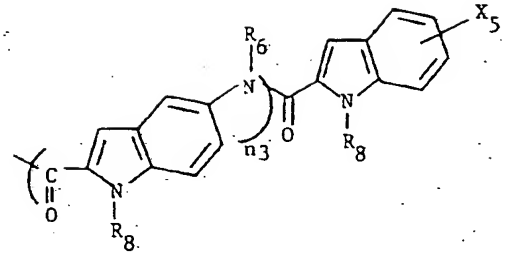
(dimer) wherein n1 = 2-12;

(vi)  where X_3 and/or X_4 = H, OH, OCH_3;

(vii)  where n2 = 1-3; and R_8 is H, CH_3 or C_2H_5;

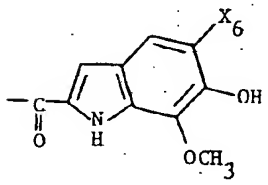
(viii)  where X_5 = H, OH, OCH_3, NO_2, NH_2, (NHAc) $NHC(O)CH_3$, $NHC(O)NH_2$; (NHBz) $NHC(O)C_6H_5$; NH-CN; and R_8 has the meaning defined above;

(ix)



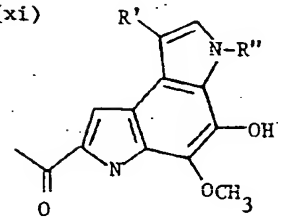
where n3 = 1, 2, or 3; and R_8, R_6 and X_5, have the meanings defined above;

(x)



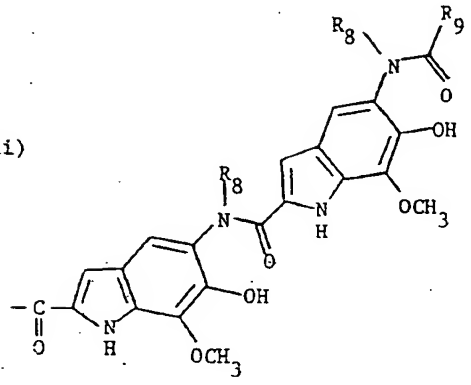
where X_6 = H, NO_2, NH_2, NHAc, $NHC(O)NH_2$;

(xi)

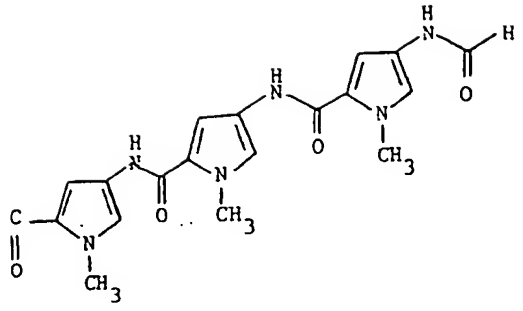


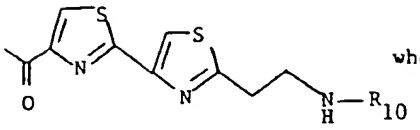
wherein R' is H or CH_3S- and R" is $NH_2(C)O$- or $CH_3C(O)$-;

(xii)



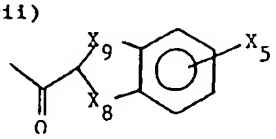
where R_8 has the meanings defined above, and R9 is $-CH_3$ or $-NH_2$;

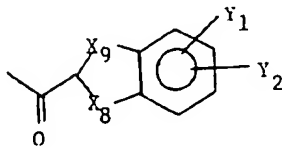
(xiii) 

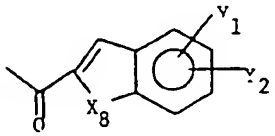
(xiv)  where R_{10} - CCH_3, CPh, H·HCl;

(xv) $-C(O)-(-R_{11}-)-C(O)-X_7-(-CH_2CH_2-X_7)n4-H$ where R_{11} - CH_2CH_2, CH=CH; and X_7 - O, NH, and n4 - 1-4, and the HCl and MeI salts for X_7 - NH;

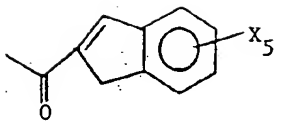
(xvi) $-C(O)-(-R_{11}-)-C(O)-X_7-(-CH_2CH_2-X_7)n4-C(O)-(-R_{11}-)-C(O)-$ (dimer) where R_7 and R_{11} and n_4 have the meanings defined above;

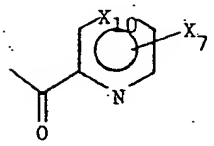
(xvii)  where X_8 is -O-, -S-, NH; X_9 is -CH= or -N=; and X_5 has the meaning defined above;

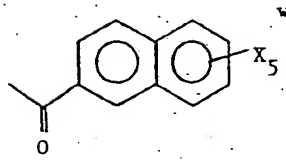
(xviia)  where X_9 and X_8 have the meanings defined above; and Y_1 and/or Y_2 - H, halo, C_1-C_4-alkyl, C_1-C_3-alkoxy, C_2-C_6-dialkylamino, nitro, amino-carbonylalkyl(C_1-C_{10}), hydroxy, amino ($-NH_2$), $-NHCONH_2$, -NHAc ($NHCOCH_3$) or-NHBz ($-NHC(O)C_6H_5$);

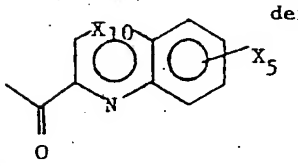
(xviib)  where X_8, Y_1 and Y_2 have the meanings

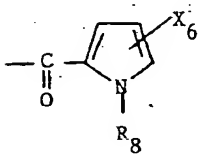
defined above;

(xviii)  where X_5 has the meaning defined above;

(xix)  where X_{10} is -CH= or -N= and X_7 is SH, NH_2, OH, H, or NHAc;

(xx)  where X_5 has the meaning defined above;

(xxi)  where X_5 and X_{10} have the meanings defined above; and

(xxii)  where X_6 and R_8 have the meanings defined above.

and when any of X_1 to X_6 is OH or NH_2, then each of the R_5 groups represented by (ii), (vi), (viii), (ix), (x), (xvii), (xviia), (xviib), (xviii), (xix), (xx), (xxi) or (xxii) are coupled with each other forming the following dimer combinations, wherein the respec-

tive R_5 groups are bound together via a oxycarbonyl (-OOC-) or an amide (-NHCO-) linkage:

ii + ii	ii + vi
ii + viii	ii + ix
ii + xvii	ii + xviii
ii + xix	ii + xx
ii + xxi	ii + xxii
vi + vi	vi + viii
vi + ix	vi + x
vi + xvii	vi + xviii
vi + xix	vi + xx
vi + xxi	vi + xxii
viii + viii	viii + ix
viii + x	xviii + xvii
viii + xviii	viii + xix
viii + xx	viii + xxi
viii + xxii	ix + ix
ix + x	ix + xvii
ix + xx	ix + xxi
ix + xxii	x + x
x + xvii	x + xviii
x + xix	x + xx
x + xxi	x + xxii
xvii + xvii	xvii + xviii
xviia + xviia	xvii + xviia
xvii + xix	xvii + xx
xvii + xxi	xvii + xxii
xviii + xviii	viii + xviia
viii + xviib	xviii + xvii
xviii + xix	xviii + xx
xviii + xxi	xviii + xxii
xix + xix	xix + xx
xix + xxi	xix + xxii
xx + xx	xx + xxi
xx + xxii	xxi + xxi
xxi + xxii	xxii + xxii

2. A compound according to Claim 1 wherein Y is selected from

hydrogen, -C(O)R, -C(S)R, -C(O)OR_1, -$S(O)_2R_1$, -C(O)NR_2R_3, -C(S)NR_2R_3, or -C(O)$NHSO_2R_4$; with the proviso that when X is a halogen atom, Y is not hydrogen.

3. A compound according to Claim 2 wherein Y is -C(O)R, -C(S)R, -C(O)OR_1, -$S(O)_2R_1$, -C(O)NR_2R_3, -C(S)NR_2R_3, or -C(O)$NHSO_2R_4$.

4. A compound according to Claim 3 where W is methyl.

5. A compound according to Claim 3 where Z is hydrogen.

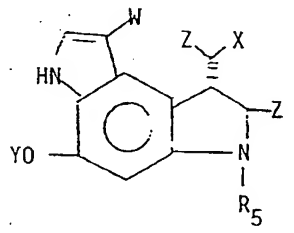
6. A compound according to Claim 3 where W is methyl and Z is hydrogen.

7. A compound according to Claim 2 where W is methyl, X is chloro and Z is hydrogen.

8. A compound according to Claim 7 where R_5 is the dimer combination viii + xviib bound together with the amide linkage.

9. A compound according to Claim 2 wherein Y is -C(O)NR_2R_3, -C(S)NR_2R_3, or -C(O)$NHSO_2R_4$.

10. A compound of formula I'a



I'a

wherein W is selected from C_1-C_5 alkyl, phenyl or hydrogen;

wherein X is selected from azido, a halogen atom, cyanate, thiocyanate, isocyanate, thioisocyanate, phosphate diester (-$PO(OR)_2$, phosphonyl (-O-PO_2R), thiophosphonyl (-O-PSOR), sulfinyl (-O-SOR) or sulfonyl (-O-SO_2R);

wherein Y is selected from hydrogen, -C(O)R, -C(S)R, -C(O)OR_1, -

$S(O)_2R_1$, $-C(O)NR_2R_3$, $-C(S)NR_2R_3$, or $-C(O)NHSO_2R_4$; with the proviso that when X is a bromo, chloro or iodo atom, Y is not hydrogen;

wherein Z is selected from the group consisting of C_1-C_5 alkyl, phenyl or hydrogen;

wherein R is selected from the group consisting of C_1-C_{20} alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, triflurомethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

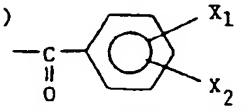
wherein R_1 is selected from C_1-C_{20} alkyl or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro;

wherein R_2 and R_3, being the same or different, are selected from hydrogen, C_1-C_{20} alkyl, or phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; with the proviso that both R_2 and R_3 can not be phenyl or substituted phenyl;

wherein R_4 is selected from C_1-C_{10} alkyl; phenyl optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro; naphthyl optionally substituted with one or 2 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, triflurомethyl, C_2-C_6 dialkylamino, C_1-C_3 alkylthio or nitro;

wherein R_5 is a carbonyl acyl group selected from the group consisting of

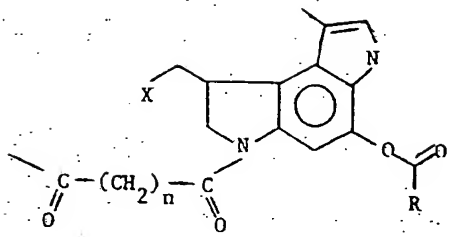
(i) $-C(O)-R_6$ where R_6 is H, -alkyl (C_1-C_{20}), $-CCl_3$, CF_3, or NH_2,

(ii)  where X_1 and/or X_2 is H, CH_3, OH, OCH_3, NO_2, NH_2, (NHNHAc) $NHNHC(O)CH_3$, (NHBz) $NHC(O)C_6H_5$, or halogen;

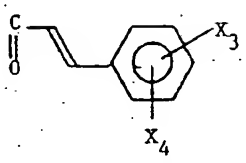
(iii) acyl derivatives ($-C(O)-CHNH_2-R_7$) of the 20 natural amino acids where R7 is the amino acid residue of glycine, alanine, valine, isoleucine, leucine, serine, threonine, aspartic acid, glutamic acid, lysine, arginine, asparagine, glutamine, cysteine, methionine, tryptophan, phenylalanine, tyrosine and histidine or proline; and their common salts selected from Na^+, K^+, NH_4^+, HCl, H_3PO_4 and (HOAc) $HOC(O)CH_3$;

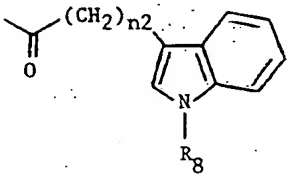
(iv) $-C(O)-CH_2CH_2-CO(C)^- M^+$ is Na, K, NH_4, or $N(CH_3)_4$;

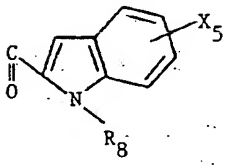
(v)

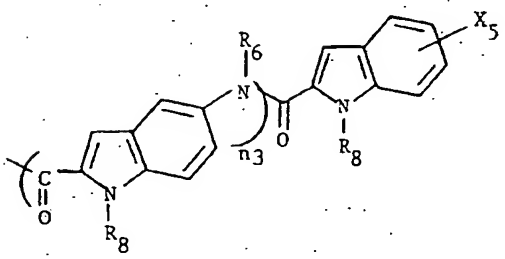


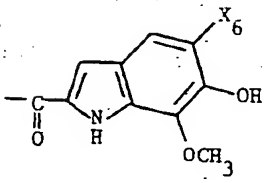
(dimer) wherein n1 = 2-12;

(vi)  where X_3 and/or X_4 = H, OH, OCH_3;

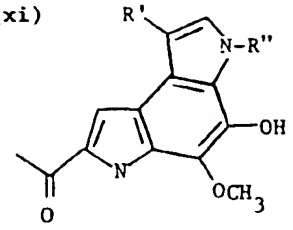
(vii)  where n2 = 1-3; and R_8 is H, CH_3 or C_2H_5;

(viii)  where X_5 = H, OH, OCH_3, NO_2, NH_2, (NHAc) $NHC(O)CH_3$, $NHC(O)NH_2$; (NHBz) $NHC(O)C_6H_5$; NH-CN; and R_8 has the meaning defined above;

(ix)  where n3 = 1, 2, or 3; and R_8, R_6 and X_5, have the meanings defined above;

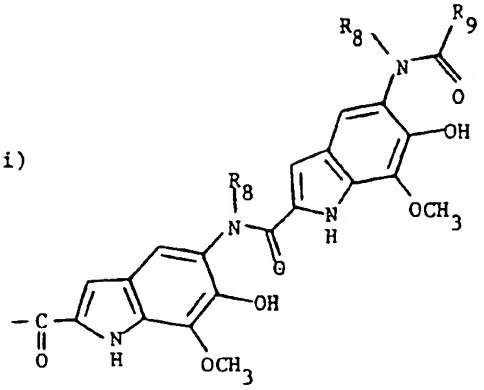
(x)  where X_6 = H, NO_2, NH_2, NHAc, $NHC(O)NH_2$;

(xi)



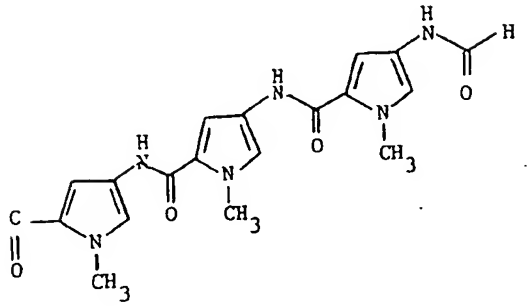
wherein R' is H or CH_3S- and R" is $NH_2(C)O$- or $CH_3C(O)$-;

(xii)

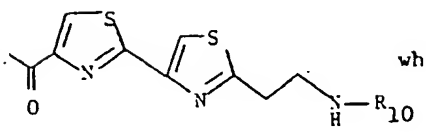


where R_8 has the meanings defined above, and R9 is $-CH_3$ or $-NH_2$;

(xiii)



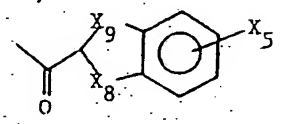
(xiv)

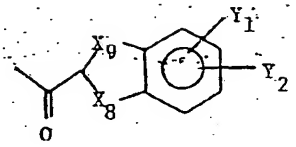


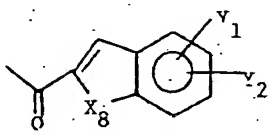
where R_{10} - CCH_3, CPh, H·HCl;
‖ ‖
O O

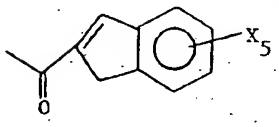
(xv) $-C(O)-(-R_{11}-)-C(O)-X_7-(-CH_2CH_2-X_7)n4-H$ where R_{11} = CH_2CH_2, CH=CH; and X_7 = O, NH, and n4 = 1-4, and the HCl and MeI salts for X_7 = NH;

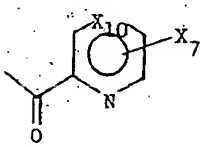
(xvi) $-C(O)-(-R_{11}-)-C(O)-X_7-(-CH_2CH_2-X_7)n4-C(O)-(-R_{11}-)-C(O)-$ (dimer) where R_7 and R_{11} and n_4 have the meanings defined above;

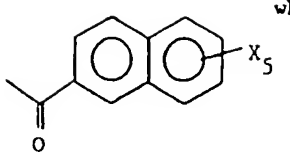
(xvii)  where X_8 is -O-, -S-, NH; X_9 is -CH- or -N-; and X_5 has the meaning defined above;

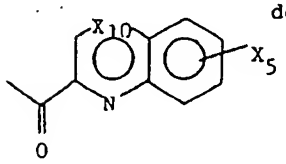
(xviia)  where X_9 and X_8 have the meanings defined above; and Y_1 and/or Y_2 = H, halo, C_1-C_4-alkyl, C_1-C_3-alkoxy, C_2-C_6-dialkylamino, nitro, amino-carbonylalkyl(C_1-C_{10}), hydroxy, amino ($-NH_2$), $-NHCONH_2$, -NHAc ($NHCOCH_3$) or-NHBz ($-NHC(O)C_6H_5$);

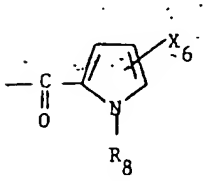
(xviib)  where X_8, Y_1 and Y_2 have the meanings defined above;

(xviii)  where X_5 has the meaning defined above;

(xix)  where X_{10} is -CH- or -N- and X_7 is SH, NH_2, OH, H, or NHAc;

(xx)  where X_5 has the meaning defined above;

(xxi)  where X_5 and X_{10} have the meanings defined above; and

(xxii)  where X_6 and R_8 have the meanings defined above.

and when any of X_1 to X_6 is OH or NH_2, then each of the R_5 groups represented by (ii), (vi), (viii), (ix), (x), (xvii), (xviia), (xviib), (xviii), (xix), (xx), (xxi) or (xxii) may be coupled with each other forming the following dimer combinations, wherein the respective R_5 groups are bound together via a oxycarbonyl (-OOC-) or an amide (-NHCO-) linkage:

ii + ii	ii + vi
ii + viii	ii + ix
ii + xvii	ii + xviii
ii + xix	ii + xx
ii + xxi	ii + xxii
vi + vi	vi + viii
vi + ix	vi + x
vi + xvii	vi + xviii
vi + xix	vi + xx
vi + xxi	vi + xxii
viii + viii	viii + ix
viii + x	xviii + xvii
viii + xviii	viii + xix
viii + xx	viii + xxi

viii + xxii	ix + ix
ix + x	ix + xvii
ix + xx	ix + xxi
ix + xxii	x + x
x + xvii	x + xviii
x + xix	x + xx
x + xxi	x + xxii
xvii + xvii	xvii + xviii
xvii + xix	xvii + xx
xvii + xxi	xvii + xxii
xviii + xviii	viii + xviia
viii + xviib	xviii + xvii
xviii + xix	xviii + xx
xviii + xxi	xviii + xxii
xix + xix	xix + xx
xix + xxi	xix + xxii
xx + xx	xx + xxi
xx + xxii	xxi + xxi
xxi + xxii	xxii + xxii

11. A compound according to Claim 10 where Y is selected from hydrogen, -C(O)R, -C(S)R, $-C(O)OR_1$, $-S(O)_2R_1$, $-C(O)NR_2R_3$, $-C(S)NR_2R_3$, or $-C(O)NHSO_2R_4$; with the proviso that when X is a halogen atom, Y is not hydrogen.

12. A compound according to Claim 11 where W is methyl.

13. A compound according to Claim 11 where Z is hydrogen.

14. A compound according to Claim 11 where W is methyl and Z is hydrogen.

15. A compound according to Claim 11 where W is methyl, X is chloro and Z is hydrogen.

16. A compound according to Claim 15 where R_5 is the dimer combination viii + xviib bound together with the amide linkage.

17. A compound according to Claim 11 selected from the group consisting of:

(S)-N-[2-[[5-(acetyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-1H-indole-2-carboxamide (Cpd #1);

(S)-N-[2-[[5-(acetyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl-2-benzofurancarboxamide (Cpd #2A);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H]indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate (Cpd #2B);

(S)-N-[2-[[5-(benzoyloxy)-1-(chloromethyl)-1,6-dihydro-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #2C);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl tetradecanoate (Cpd #2D);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl decanoate (Cpd #2E);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl dodecanoate (Cpd #2F);

(S)-N-[2-[[1-(azidomethyl)-1,6-dihydro-5-hydroxy-8-methyl-benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #6);

(S)-N-[2-[[5-(benzoyloxy)-1-(bromomethyl)-1,6-dihydro-8-methyl-benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl] 2-benzofurancarboxamide (Cpd #2G);

(S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']di-pyrrol-4-yl decanoate (Cpd #3);

(S)-6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']di-

pyrrol-4-yl tetradecanoate (Cpd #4); or

(S)-6-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydro-5-hydroxy-4-methoxybenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b:4,3-b']dipyrrol-4-yl hexanoate (Cpd #5);

(S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenylamino)carbonyl]oxy]benzo[1,2-b:4,3-b']dipyrrol-3(2)-yl]carbonyl]-1H-indol-5-yl]-2-benzofurancarboxamide (Cpd #10A);

(S)-3-[[6-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, butyl carbamic acid (Cpd #10B);

(S)-3-[[6-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 3,4-b']dipyrrol-4-yl ester, 2,2-dimethyl propanoic acid (Cpd #10C);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, [4-(trifluoromethyl)phenyl]-carbamic acid (Cpd #10D);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-2-methyl]benzo [1,2-b 4,3-b']dipyrrol-4-yl ester, (3,5-dimethylphenyl)-carbamic acid (Cpd #10E);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, (4-chlorophenyl)-carbamic acid (Cpd #10F);

(S)-6-[[5-[(2-benzofuranylcarbonyl)amino]-1H-indol-2-yl]-carbonyl]-8-(chloromethyl)-3,6,7,8-tetrahydro-1-methylbenzo[1,2-b 4,3-b']dipyrrol-4-yl ester, (3,4-difluorophenyl)-carbamic acid (Cpd #10G);

(S)-8-(chloromethyl)-6-[[5-[[[6-(diethylamino)-2-benzofuranyl]-carbonyl]amino]-1H-indol-2-yl]carbonyl]-3,6,7,8-tetrahydro-1-methyl-benzo[1,2-b 4,5-b']dipyrrol-4-yl ester, 2,2-dimethyl-propanoic acid (Cpd #11A);

(S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenylamino)carbonyl]oxy]benzo[1,2-b 4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-6-(diethylamino)-2-benzofurancarboxamide (Cpd #11B).

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(74) Agent: JAMESON, William, G.; Patent Law Department, The Upjohn Company, Kalamazoo, MI 49001 (US).

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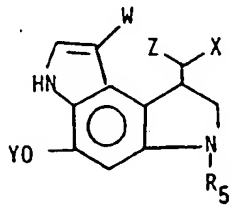

(I)

(57) Abstract

2-Acyl-4,5,8,8a-tetrahydro-4-oxycyclopropan[c]pyrrol(3,2-e) indole derivatives of Formula (I'). The compounds of Formula (I') are useful as uv light absorber substances, as chemical intermediates and as prodrugs of known spirocyclopropylpyrroloindole CC-1065 analogs. Representative Formula (I') compounds have been shown to possess useful ranges of antitumor activity in standard laboratory animal tests.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/03227

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 487/04; 519/00; C 07 F 9/65, //
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II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0154445 (UPJOHN) 11 September 1985 see the whole document cited in the application --	1
P,X	Journal of the American Chemical Society, volume 109, 28 October 1987, American Chemical Society, (Washington, US), R.C. Kelly et al.: "Coupling of cyclopropapyrroloindole (CPI) derivatives. The preparation of CC-1065, ent-CC-1065, and analogues", pages 6837-6838 see scheme II --------	1

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Classification System	Classification Symbols
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0154445	11-09-85	JP-A- 60193989	02-10-85